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ACTA PHYSIOLOGICA SCANDINAVICA
VOL. 50. SUPPLEMENTUM 176.

COMPARATIVE STUDIES ON THE ADRENERGIC NEURO-HORMONAL CONTROL OF RESISTANCE AND CAPACITANCE BLOOD VESSELS IN THE CAT

BY

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VOL. 50. SUPPLEMENTUM 176.

FROM THE DEPARTMENT OF PHYSIOLOGY, UNIVERSITY OF GÖTEBORG,
GÖTEBORG, SWEDEN

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STEFAN MELLANDER

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CHAPTER I

General introduction

The neuro-hormonal control of blood flow through the various systemic 'parallel-coupled' vascular sections supplying the different tissues has been extensively studied (for ref. see FOLKOW 1956 a). Most earlier investigations have, however, generally only given qualitative aspects of regional blood flow regulation in different organs. More recently this subject has also been studied from a quantitative point of view (*e. g.* FOLKOW 1952 a, CELANDER and FOLKOW 1953, CELANDER 1954), thus providing a better insight into the true range of neuro-hormonal control of the resistance to flow. However, even this approach gives only a limited insight into the complex functional characteristics of a vascular bed. Each circuit has not only 'resistance vessels' but can in fact be divided into the following functionally defined 'series-coupled' sections (see also FOLKOW 1959):

a. '*Windkessel vessels*', transforming the pulsatile cardiac outflow into a fairly steady flow through the smallest blood vessels.

b. '*Resistance vessels*', mainly consisting of two variable sections — a precapillary (predominantly the arterioles) and a postcapillary one (predominantly the small veins) — which determine changes of the resistance to flow and also affect the hydrostatic capillary pressure and hence the filtration exchange across the capillary walls.

c. '*Sphincter vessels*', a specialized section of the smallest precapillary resistance vessels, where smooth muscle sphincters can induce intermittent luminal closure, thus regulating the size of the capillary surface area available for flow, and hence for blood-tissue exchange.

d. '*Shunt vessels*', present in some tissues only, permitting a by-pass of the 'exchange vessels'.

e. '*Capacitance vessels*' [1]), (mainly the veins) in which even minor changes in smooth muscle tone, too small to influence the resistance to flow significantly, will induce haemodynamically highly important shifts in blood distribution and adjust the circulating blood volume available for the 'pump'.

[1]) The terms 'resistance' and 'capacitance', both commonly used in electronics, have here been used, since the functional characteristics of an electrical circuit are in many respects analogous to those of a vascular circuit.

All these functionally specialized vascular sections include smooth muscle structures in their walls and are subordinated to autonomic neuro-hormonal control. They are all, to a greater or lesser extent, engaged in the control of flow through the most important peripheral vascular section, *i. e.*

f. The *'exchange vessels'*, or the true capillaries, the section for the direct exchange between blood and tissue, which thus fulfils the ultimate aim of cardiovascular function. These vessels are devoid of smooth muscle cells.

A functional distinction of the different 'series-coupled' sections of the vascular bed, as indicated above, implies obvious advantages from a physiological point of view. It should be realized, however, that it cannot be directly correlated to existing morphological definitions of the vessels, as certain overlaps exist; but it can be said that the smallest arterial vessels constitute the most important resistance section and that the veins dominate the capacitance section. Thus, the venous side of the circulation has been calculated to contain up to 70 per cent of the total blood volume, whereas the arterial vessels hold only about 15—20 per cent; the capillaries contain approximately 5—10 per cent and the heart about 5—10 per cent (GREEN 1950, p. 228). More recent studies also indicate that by far the largest fraction of the blood volume is contained in small blood vessels, especially venules and other smaller veins (KNISELY, MAHALEY and JETT 1958, MILNOR and BERTRAND 1958).

A complete analysis of the neuro-hormonal control of a vascular bed should thus not be limited only to a study of the gross reactions of the resistance vessels in terms of changes in peripheral resistance, as has hitherto usually been the case. More detailed studies of the reactions of the above-mentioned various vascular sections are also required. It would, for instance, be of fundamental importance to differentiate *quantitatively*, in one and the same tissue, between the relative influence of neuro-hormonal mechanisms on the smooth muscles of the various 'series-coupled' vascular sections, as these sections are in many respects functionally specialized and hence may be unequally affected.

Mention may here be made of some problems in this connection which have been approached experimentally in the present study. Since the ratio between pre- and postcapillary resistance is one of the main determinants of hydrostatic capillary pressure, neuro-hormonally induced changes in this ratio will be of great importance for the filtration exchange between blood and interstitial fluid (see PAPPENHEIMER 1953). Further, the relative potency of the neuro-hormonal control of the capacitance vessels will determine the range of centrally induced rapid redistributions of blood volume, *e. g.* to augment cardiac output, to compensate for blood pooling or blood losses, etc. Moreover, neuro-hormonally induced changes of tone in the precapillary sphincters, which will

be dealt with in another study (FOLKOW and MELLANDER 1960), will in many important respects influence the exchange taking place between blood and tissue across the capillary walls. A closure of a fraction of the precapillary sphincters will not only reduce the capillary surface otherwise open to exchange, but also increase the mean diffusion distance from blood to tissue cells. Further, it may even reduce the time available for exchange, if the number of capillary tubes open to flow becomes relatively more reduced than the volume flow through the tissue. This will lead to increased linear flow velocity through the still open channels of the capillary section. Thus, changes of tone in these smooth muscle sphincters may directly or indirectly affect most of the factors governing the important diffusion exchange between blood and tissue according to FICK's law (see PAPPENHEIMER 1953). Precapillary sphincter closure will, of course, also affect filtration exchange.

Many important problems arise when the vascular bed is considered from this point of view. Does, for instance, the sympathetic influence on the various vascular sections affect them all in an undifferentiated way, giving an overall similar and simultaneous effect, or do quantitative or even qualitative differences exist between the consecutive parts of the vascular bed, with regard to their central and local control? It should be borne in mind here that differences between the sections concerning nerve fibre distribution, discharge rates, effector sensitivity to excitatory and inhibitory influences, and wall/lumen ratios may all contribute to the differentiation of the effector responses. A closer insight into the complicated integration of the cardiovascular system is possible first when the range of control over each section is analysed and known in detail, a fact which is now being more and more realized.

Much interest has thus in recent years been focused on the control of the veins (see for instance the review by LANDIS and HORTENSTINE 1950). Their great importance for the filling of the 'pump' has been elucidated in a number of investigations (*e. g.* RASHKIND *et al.* 1953, GAUER 1956, GAUER and HENRY 1956, ROSE and FREIS 1957, GUYTON, LINDSEY and ARMSTRONG 1956 and GUYTON *et al.* 1958). — It is, however, somewhat complicated to study in detail the reactions of the peripheral veins without interfering with normal cardiovascular dynamics. It has previously often been necessary to use indirect qualitative or at best semiquantitative methods, most of them based on pressure recording in more or less restricted and isolated venous segments. In some cases such preparations have been utilized where normal circulation through the vascular bed must have been seriously disturbed. In spite of this, a number of interesting data have been presented which seem to make it evident that the veins, at least under certain circumstances, respond in a

similar way to autonomic nervous influence as do the resistance vessels. Thus, to mention a few of the more recent investigations, DONEGAN (1921) demonstrated a constriction in terms of increased pressure or reduced flow in isolated cutaneous and mesenteric venous segments when the sympathetic nerves were directly stimulated. KELLY and VISSCHER (1956) and SHADLE, ZUKOF and DIANA (1958) recorded in perfusion experiments on dogs a decrease in hind paw volume and hind limb weight respectively, at high frequency sympathetic stimulation. This was interpreted as being caused by a constriction within the venous system. — Reflex activation of the smooth muscles of the veins has been demonstrated by different techniques. In studies of venous resistance to flow, FLEISCH (1931) found that a constriction occurred in isolated splanchnic veins with intact nerve supply on occlusion of the common carotid arteries and when the carbon dioxide tension in the blood was increased. The participation of the venomotor system in pressor reflexes or during haemorrhage has further been studied by, for example, ALEXANDER (1954, 1955), who analysed pressure-volume curves in the splanchnic veins and by SALZMAN (1957), who recorded pressure variations in a miniature balloon inserted in a peripheral superficial vein in dogs. GUYTON and coworkers (1956, 1958), again, have utilized measurements of 'mean circulatory pressure' for the evaluation of reflex shifts of tone in the 'capacitance vessels', in a way an isometric recording of their smooth muscle contractions. — It has further been found that various stimuli can also elicit venomotor reflexes in the human being. Such reflexes have generally been demonstrated by recording pressure changes in small, temporarily isolated superficial veins, *e. g.* by DUGGAN, LOVE and LYONS (1953), PAGE *et al.* (1955) and BURCH and MURTADHA (1956).

There is evidence that also the 'hormonal link' of the sympatho-adrenal system affects the venous side. Thus for instance WALLACE and STEAD (1957) demonstrated increments of venous pressure in the human hand and forearm during noradrenaline infusion. GLOVER *et al.* (1958) recorded a decrease in volume of the human hand and forearm at noradrenaline and adrenaline infusion during graded venous congestion, interpreted as being due to constriction of the venous capacitance vessels.

Although these earlier investigations on veins have given important information about neuro-hormonal influences on the capacitance vessels, there are so far practically no quantitative data concerning the exact range of the capacitance vessel control as exercised by the sympathetic nervous system or by blood-borne and local chemical factors, especially not in comparison with the control of the resistance vessels.

The present study was undertaken in order to investigate, both qualitati-

vely and quantitatively, the neuro-hormonal control of the capacitance vessels, as compared with that of the pre- and postcapillary resistance vessels. It was performed both on a combined skin-muscle and a more isolated muscle region. There is reason to believe that the method used in this study allows simultaneous and selective studies of the haemodynamic effects induced in the different 'series-coupled' sections of the vascular bed; and further, that these studies can be carried out without interfering too much with normal cardiovascular reactivity and dynamics.

A brief preliminary description of this study has previously been presented in other connections (see FOLKOW 1959, MELLANDER 1960).

CHAPTER II

Method

1. General considerations

It is evident that for a study of the control of the resistance vessels, recording of perfusion pressure and blood flow is indispensable. As for the capacitance vessels,changes of tone would considerably affect the amount of blood present in the vascular region. There are many possible ways of measuring the blood volume contained in a vascular bed, but only a few of these are suitable for recording continuously rapid, phasic shifts of the blood content. This is necessary if, for example, the nervous control of the capacitance vessels is to be compared with that of the resistance vessels. However, tissues which are not enclosed in rigid structures will vary in total volume, or weight, with the amount of blood contained in their vascular beds. A continuous measurement of the volume or the weight respectively of the tissue mass will thus offer a possibility of following the variations in the tone of the capacitance vessels, provided other influencing factors can be kept under control and artefacts excluded. The weight and the volume will, however, also vary with shifts in extravascular fluid volume, occurring across the capillary walls, and it would *a priori* appear difficult to differentiate between intravascular and transvascular fluid shifts. These two dynamic phenomena show, however, such different time characteristics that a clear distinction between them seems quite possible. If, for instance, blood composition with regard to colloid osmotic pressure is kept fairly constant, and arterial and venous pressures are so controlled that shifts in effective capillary pressure become relatively small, the net filtration across the capillary walls will be negligible. It is known from other investigations that the rate of filtration across the capillary walls is quite slow, *e. g.* in skeletal muscles about 0.01—0.02 ml/mm Hg/min/100 g tissue (see PAPPENHEIMER 1953). The phasic changes in the smooth muscle tone of the capacitance vessels, on the other hand, should occur rapidly, and give rise to considerable changes in volume or weight, within a fraction of a minute. It can thus be assumed that a change in the tone of the vascular smooth muscles will induce rapid changes not only in blood flow but also in total regional amount of blood, thereby affecting tissue volume[1]) considerably.

[1]) The term 'tissue volume' refers below to the total volume of the hind parts of the cat.

Variations in effective capillary filtration pressure, on the other hand, will give rise to relatively slow but more continuous volume changes.

On the basis of these considerations and the favourable experience of a similar type of measurement used by PAPPENHEIMER and SOTO-RIVERA (1948) in their classical study of fluid exchange across capillary walls, the following principle of method was elaborated (for details see section 2 of this chapter). A suitable part of the animal was 'isolated' from the main part of the body so that only its sympathetic nerve supply and its cognate artery and vein were left intact. The arterial inflow pressure was measured and on the venous side a flow meter was inserted in such a way that it also simultaneously made a continuous measurement of the venous outflow pressure possible. Changes in the volume of the tissue part studied were recorded by a sensitive plethysmographic technique and the regional blood volume present at a given moment of steady state, was measured by means of a radioactive isotope dilution technique. — The investigated tissue area was thus in a normal way supplied with oxygenated blood from the heart *via* the intact cognate arteries, and central vasomotor fibre control was largely unaffected as long as the sympathetic nerves of the studied region were left intact. The nerves could also be isolated and cut centrally to allow direct stimulation.

Thus the pressure head across the vascular bed studied could be kept under strict control by adjusting inflow pressure and/or outflow pressure to desired levels. Changes in blood flow could be continuously recorded and phasic shifts in regional blood volume and transcapillary filtration exchange, respectively, could be deduced from the continuously recorded changes in tissue volume. This technique would thus permit simultaneous observations of at least some of the haemodynamic reactions of the pre- and postcapillary resistance vessels and the capacitance vessels, together with net fluid shifts across the walls of the 'exchange vessels'.

2. Details of experimental procedures

In most experiments the total hind parts of the animal below the level of the anterior superior spines of the pelvis constituted the tissue area selected, for this study. It thus mainly included skin, skeletal muscle, and bone tissue in weight proportions of about 1 : 4 : 1 respectively. Since the skeletal tissue, here containing mainly yellow bone marrow, is of minor importance in this connection, this preparation will be referred to as a 'combined skin-muscle region'. However, experiments were also performed on a purer muscle preparation, in which the limbs had been skinned and the tail and paws excluded

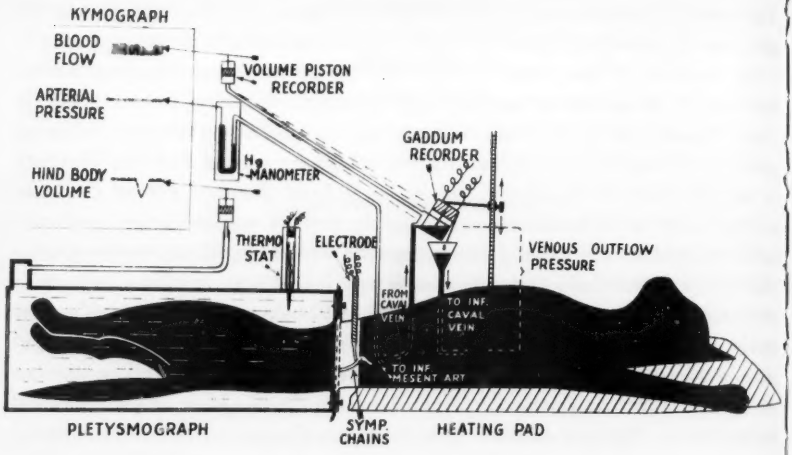

Fig. 1. Schematic illustration of the method and preparation used. Vascular reactions studied in the cat's hind parts supplied with oxygenated blood from intact lungs, heart and arterial connections. Arterial inflow pressure and venous outflow pressure kept constant. Total blood flow in the region recorded by a Gaddum recorder providing information of the reactions in the resistance vessels. Volume of hind parts recorded plethysmographically using a circular segment of the abdominal skin for closure of the plethysmograph. Rapid changes in volume of the region reflected phasic variations in blood content of the regional capacitance vessels, while an isotope technique gave steady state figures of the total contained blood volume. Characteristically slower changes of volume in the hind parts reflected net variations in capillary filtration.

from the circulation by tight ligatures. This preparation is called below a 'muscle region'.

The technique and experimental arrangements are schematically illustrated in Fig. 1.

a. Material. Experiments were performed on a total of 87 cats. 65 animals were used for studying the sympathetic vasoconstrictor fibre control, 8 of these being prepared for studies on a muscle region. In 22 cats the vascular effects of the adrenergic hormones, released from the adrenal medulla, were also studied in comparison with the influence of the direct vasomotor innervation, 9 of these being prepared for studies on a muscle region.

b. Anaesthesia. In most experiments in which sympathetic nervous effects were studied, the cats were anaesthetized with chloralose (50 mg/kg) and uretane (100 mg/kg) given intravenously, but in a few animals dial (Ciba, 30—40 mg/kg), or uretane alone (1 000—1 500 mg/kg), was used. In experi-

ments dealing with effects of blood-borne catechol amines, dial or uretane was more frequently used. Both these anaesthetics, particularly uretane, are said to interfere much less than chloralose with the vasodilator effect of adrenaline in skeletal muscle tissue (see LUNDHOLM 1957).

c. Operative procedures. A tracheal cannula was inserted, and in about 50 per cent of the experiments artificial respiration was given, adjusted to a level that barely suppressed the spontaneous respiration of the animal. It was given in order to avoid interferences of possible changes in spontaneous respiration. — After clipping the fur of the hind parts of the animal closely to the skin, the abdomen was opened in the midline and in the majority of the experiments, the small intestines and the colon were extirpated in order to get free access to the aorta, the caval vein and the abdominal sympathetic chains. Care was taken not to damage the arterial supply or the venous drainage of the remaining abdominal organs. In a small series of experiments (3 animals), the intestines were left intact. The aorta and the inferior caval vein were isolated from a level just below the kidneys down to the aortic and caval vein bifurcations and minor vascular branches in this region were divided between ligatures. The two abdominal sympathetic chains, containing practically all the vasomotor fibres supplying the hind parts, were carefully isolated at the height of the fourth and fifth lumbar vertebrae, where all preganglionic fibres have reached the sympathetic cha ns but very few of the postganglionic fibres of the studied region have left (REIGHARD, JENNINGS and ELLIOTT 1949, p. 404). The sympathetic chains could later on be cut just proximally to the ganglion at the fourth lumbar vertebra to allow direct electrical stimulation of their peripheral ends. Sympathetic stimulation at this level will thus excite the great majority of the vasomotor fibres supplying the isolated hind parts. In this way the hind parts could be deprived of their centrally induced vasomotor tone, and the smooth muscles of the vessels could be exposed to the influence of constrictor fibre activity by graded electrical stimulation of the peripheral ends of the two sympathetic chains.

To be able to record the total blood flow through the hind parts (see below), it was necessary to be sure that the inferior caval vein remained absolutely the only pathway of venous return from the region. As several venous collaterals exist, all the tissues at the height of the plane through the anterior superior spines were therefore ligated in small portions down towards the disc between the fourth and fifth lumbar vertebrae. In all but 3 animals, vessels along and inside the spinal medulla were also occluded by plugging the spinal channel at the same level with cotton wool soaked in wax. This also secured a complete interruption of all somato-motor fibres to the studied region, while the post-

ganglionic sympathetic pathways were left essentially intact. With the exception of the aorta, the inferior caval vein and the sympathetic nerve supply, the only structures left intact by this circular 'division' of the animal were the two ureters. A free urine drainage from the kidneys was secured by a cannula inserted through the urinary bladder wall. The anus was closed with sutures, and the urethra, and in female cats also the vagina, was ligated. The last arrangements were required in order to avoid undesired interference in the volume recording of the hind parts from volume changes occuring in the bladder, the uterus and the small remaining part of the rectum. Late in the course of the preparation the right adrenal gland was extirpated and the left one denervated in those experiments where it was desirable to avoid any reflex release of adrenaline and noradrenaline into the blood stream. Bleeding from the tissues was carefully avoided and if blood losses occurred they were substituted by intravenous injections of dextrane[1]) Tyrode solution. The body temperature of the cat was maintained at 38° C by a heating pad placed under the animal and an infra-red lamp above it.

d. Recording of the tissue volume.[2]) The hind parts of the cat were placed horizontally inside a cylindrical perspex plethysmograph through a well-fitting opening at its proximal base. The skin on the lower part of the abdomen was circumcised and its distal part freed from the underlying tissue as to form an inch-wide skin segment around the body. Small circular holes were cut in the periphery of this skin segment to fit six screws placed around the opening of the container. The skin was fixed on the screws and arranged smoothly towards the greased base of the cylinder. It was important here not to stretch the skin of the studied region too much, in order to avoid abnormal tension on the tissues. A perspex flange in two parts was then placed outside the fixed skin segment, which was thus firmly pressed between the two perspex surfaces by screws. By this arrangement the hind parts were enclosed in the container in a perfectly waterproof way, without interference with the arterial inflow or venous outflow. The container was filled with water at 38° C temperature *via* a stopcock, leaving only a small air volume in a chamber at the top of the plethysmograph. The stopcock was closed and an outlet from the chamber was connected to a volume piston recorder. The temperature of the water could be regulated thermostatically by an infra-red lamp to the desired level, usually kept at 36—38° C.

In 8 cats studies were performed on a more selective skeletal muscle region. The hind parts were then skinned and the circulation through the paws and the tail was excluded by tight ligatures around the ankles and the root of the

[1]) I am indebted to AB Pharmacia, Uppsala, Sweden for a generous supply of Dextran.
[2]) See footnote on p. 10.

tail respectively. A two-inch-wide segment of skin was left on the proximal part of this tissue region and used for closure of the plethysmograph. The exposed surface of the muscle tissue was sprayed with Nobecutan (Bofors-Nobelkrut)[1]), forming a thin plastic film to protect the tissue. In these experiments the plethysmograph was filled with Tyrode solution.

e. Blood flow recording. The animal was heparinized and two cannulae were inserted into the freed part of the inferior caval vein, one in its distal end, shunting venous outflow from the hind parts to a modified Gaddum blood flow recorder, and the other in its proximal end, for automatic return of the blood from the recorder, *via* a funnel, into the animal. Cooling of the blood, when stored in the funnel for a short period of time, was prevented by an infra-red lamp placed above the Gaddum recorder. Siliconized wide bore cannulae and tubings were used to minimize the added resistance to flow and to avoid damage of the blood cells. The operative procedure for inserting the blood flow recorder (when blood flow through the region was stopped), required less than five minutes. The rate of venous outflow from the hind parts could then be continuously measured by the Gaddum recorder, connected to a volume piston recorder. The ordinates of the recording system are directly proportional to the rate of blood flow, within reasonable limits. As a check, the rate of venous outflow was also measured directly at intervals by a stop-watch and a graded test tube. The time ratio between the closed (collecting) phase and the open (emptying) phase of the Gaddum recorder was approximately 12 to 1. The period of the closed phase could be varied from three seconds down to half a second, thus permitting even large blood flows and rapid flow changes to be recorded adequately.

The animals could, after this preparation, be kept in a satisfactory circulatory state for several hours and blood samples collected for centrifugation at the end of the experiments revealed that haemolysis of the red cells did not occur.

f. Pressure recordings. Mean arterial 'inflow pressure' was recorded with a mercury manometer connected to the proximal end of the inferior mesenteric artery. As for instance the activation of the vasomotor fibres will to some extent affect the arterial pressure, the perfusion pressure of the hind parts could be kept constant during vasomotor fibre stimulation, either by adjusting a screw clamp applied around the aorta just proximally to the inferior mesenteric artery, or simply by adjusting the venous return to the animal from the funnel of the Gaddum recorder. Thus arterial pressure

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[1]) I am indebted to AB Bofors-Nobelkrut, Bofors, Sweden for a generous supply of Nobecutan.

changes, which will interfere with the recorded vasoconstrictor responses, could be eliminated if desired.

Venous pressure at the outflow end of the inferior abdominal caval vein was controlled simply by the vertical level above the heart at which the Gaddum recorder was mounted. Since the hind parts were enclosed in a water bath, there was a small external pressure applied to the tissue, which would slightly increase the net transfer of tissue fluid to the blood stream in the enclosed area, resulting in a slow continuous decrease of the recorded tissue volume at 'rest', if venous outflow pressure were not raised proportionally. Therefore the flow recorder was slightly elevated above the heart level, so increasing the intravascular hydrostatic pressure as to re-balance the net transfer of fluid at the capillary level to zero and so restore the 'isovolumetric state'. — The above-mentioned compensation of the venous outflow pressure level could thus easily accomplish a zero net transfer of tissue fluid in the *total* hind parts, although presumably in some areas a slight absorption of fluid might occur with a corresponding filtration from the vessels in other areas; but such regional differences also exist, of course, normally.

When an isovolumetric state was once achieved in the 'resting' animal, the adjusted venous outflow pressure and the arterial inflow pressure could, if desired, be kept unchanged throughout the experiment. Thus, flow and volume changes caused by variations in arterial inflow pressure and venous outflow pressure could be effectively excluded. The observed variations of blood flow and tissue volume could therefore be regarded as true indicators of induced changes of smooth muscle tone in the vascular bed.

g. Blood volume determination. Blood volume determinations were made according to the isotope dilution principle, using Cr^{51}-labelled red cells (Grey and Sterling 1950) prepared from the cat's own blood. Blood samples were withdrawn and analysed for Cr^{51}-activity and haemoglobin. From the amount of Cr^{51}-activity injected and the observed Cr^{51}-activity per unit haemoglobin at equilibrium, the total amount of haemoglobin (THb) was determined. The blood volume was estimated from the THb and the haemoglobin concentration. No correction was made for different haemoglobin concentrations in different vascular sections.

The blood volume contained in the hind parts of the cat was determined according to the following procedure: Cr^{51}-labelled red cells were injected into the superior caval vein *via* a catheter inserted into the right external jugular vein, after the aorta and inferior caval vein had been occluded simultaneously so that circulation through the hind parts of the animal was temporarily stopped completely. Blood samples were withdrawn through another fine catheter, advanced to a site near the heart *via* the left external jugular

vein, at intervals during a 20 min period after the isotope injection. The occluding clamps on the aorta and caval vein were then removed, allowing the labelled cells to mix with blood in the hind parts of the cat also. New blood samples were withdrawn at intervals during another 20 min period and all samples were then tested in duplicate on haemoglobin and Cr^{51}-activity. 10 minutes after the injection of the Cr^{51}-labelled cells and 10 minutes after the removal of the occluding clamps on the aorta and the caval vein, 5μ g of noradrenaline was injected intravenously to facilitate perfect mixing of the labelled cells also with blood stored in depot regions. The blood volume in the upper part of the cat, as well as the total blood volume of the animal, could thus be selectively estimated, as could the amount of blood in the hind parts on the basis of the other two values. — It was important to check that no collaterals were left between the hind parts and the main part of the cat during the period of aortic and caval vein occlusion. This was done by means of an experiment similar to that described in detail on p. 24: the vasoconstrictor fibres of the hind parts were stimulated during the occlusion period, but no change in volume of the hind parts then occurred. If any venous collaterals had been left, tissue volume should have decreased, since part of the blood stored in the vascular bed had then been pushed out *via* such collaterals. The absence of collaterals, especially arterial ones, in this type of preparation was further proved in a few experiments where only the blood volume of the upper part of the body was measured: as long as the aorta and the caval vein were occluded no radioactive substance could be traced in blood samples withdrawn from the isolated vascular bed of the hind parts. — The estimation of the blood volume contained in the isolated hind parts could be performed at any desired moment during the experiment. It was always made when the preparation was in a steady, isovolumetric state with a stable blood flow and stable inflow pressure and outflow pressure.

For a complementary study of the regional blood volume another method was used. In the steady state the abdominal aorta and inferior caval vein were occluded simultaneously and then the hind parts were rapidly perfused with a fixed large quantity of dextrane Tyrode solution. By determining the haemoglobin dilution hereby obtained, the regional blood volume thus 'washed out' could be approximately estimated. This method will be referred to as the 'Hb-dilution method'.

h. Stimulation of the sympathetic vasoconstrictor fibres. The peripheral ends of the two lumbar sympathetic chains were placed at equal level on a bipolar platinum electrode and immersed in an insulating and protecting bath of paraffin oil, the temperature of which was kept at 38° C. A Grass stimulator, model S4E, was used, delivering square wave stimuli, where

frequency, voltage and pulse duration could be set at any desired value. A maximal vascular response to stimulation at a given frequency was in most cases obtained at a voltage of 3, and a pulse duration of 1 msec. Supramaximal stimulation voltage was always applied in order to secure excitation of all vasoconstrictor fibres. When only the effect of the vasoconstrictor fibres was to be studied, the sympathetic cholinergic vasodilator fibres leading to the skeletal muscles were blocked by a slow intravenous injection of atropine, 0.3—0.4 mg/kg bodyweight, in order to eliminate the interfering vasodilator effect caused by activation of these fibres.

i. Stimulation of the sympathetic secretory nerves of the adrenal medulla. In experiments where the effects of catechol amines released from the adrenal medullae were to be studied, the greater and the lesser splanchnic nerves on the left side, and in a few cases also on the right side, were dissected free of surrounding tissue and cut centrally. The isolated nerves were placed on bipolar platinum electrodes and stimulated simultaneously by the same technique as described above. However, owing to the technical difficulties and major operations involved in isolating the secretory nerves of the right adrenal medulla, as they run behind the liver, this gland was excluded from the circulation in most experiments by enclosing ligatures. Thus only the left splanchnic nerves were stimulated in most experiments, but then at the *double* frequency used for corresponding stimulations of the two sympathetic chains. This was justified, as the amount of catechol amines released at sympathetic excitation in general appears to be proportional to the stimulation frequency also when supraphysiologic frequencies are used provided the period of stimulation is less than about 2 minutes and the frequency used does not exceed 30—40 impulses/sec (see ROSENBLUETH 1950, p. 88, FOLKOW 1952 a). Further, there is at least indirect evidence that the amount of catechol amines liberated from one adrenal, when all the cells are excited, approximately equals half the amount released from both glands when subjected to a given frequency of splanchnic stimulation (see CELANDER 1954). — In cats exposed to maximal *reflex* sympathetic excitation, some 2—3 μg/kg/min of mixed catechol amines have been estimated to be released. During splanchnic stimulation at maximal 'physiological' rate (10 impulses/sec) an average figure of as much as 5 μg/kg/min is released (CELANDER 1954). Individual variations do naturally occur in different stimulation experiments, but these data form a reasonable basis for adjusting the dosage of adrenaline and noradrenaline in the infusion experiments (see chapter V).

j. Infusion of catechol amines. Solutions of l-adrenaline hydrochloride and l-noradrenaline hydrochloride were prepared with Tyrode solution with pH adjusted to 7.3. The catechol amines are expressed as HCl salts in all data

concerning dosage given below. These solutions were kept in an ice bath and warmed up to 37° C just before infusion. In a first series of experiments (15 animals) adrenaline and noradrenaline was infused intravenously *via* a fine catheter inserted into the left brachial vein. This means of administration then simulated that which normally occurs in the intact organism when catechol amines are released from the adrenal medullae and secreted into the venous blood stream. In an additional study (7 animals) the catechol amines were also given by close arterial infusion *via* a catheter inserted into the central end of an isolated lumbar artery. This procedure made it possible to estimate more exactly the amounts of catechol amines reaching the studied region. Constant infusion rates were achieved by a motor-driven infusion apparatus.

k. Plasma protein analysis was performed according to the Kjeldahl method.

CHAPTER III

Experimental analysis of method

Since the method used in this study has not previously been tried for an approach to the integrative control of resistance and capacitance blood vessels, an experimental analysis of what was actually recorded has been undertaken.

Fig. 2 *A* illustrates at a 'steady state' the tracings of the three parameters which were regularly recorded on the kymograph in the present series of experiments, namely the arterial perfusion pressure, the volume changes and the blood flow in the hind parts of the cat. The arterial inflow pressure[1]) of the studied region was usually kept as constant as possible during the course of each experiment. The height of the ordinates in the blood flow tracing is directly proportional to the rate of blood flow. As the perfusion pressure head remains fairly constant, the height of the ordinates will be approximately inversely proportional to regional peripheral resistance. – The method of recording volume changes in the hind parts proved to be so sensitive that the characteristics of each arterial pulse wave were clearly reflected in the volume tracing. The Gaddum recorder was mounted at such a height above the heart level that the venous outflow pressure of the hind parts exactly balanced the normal caval venous pressure and also the external pressure added by the water in the plethysmograph, otherwise a continuous baseline drift of the volume recording occurred (see also p. 16). Thus, an isovolumetric state was achieved during 'resting' conditions, manifested by an equilibrium in tissue volume and represented by a horizontal tracing of the volume of the hind parts. When the isovolumetric state was once established 'at rest', a slight additional increase in venous outflow pressure evoked a characteristic response (Fig. 2 *B*). There was first a small abrupt but transient increase in volume, followed by a definitely slower but continuous one. These two changes in volume show completely different slope characteristics in the record. If, on the other hand, venous outflow pressure was decreased below the level representing the isovolumetric state, analogous phenomena

[1]) The pressure level is indicated in the figures by horizontal calibration lines, each placed at an interval of 20 mm Hg. One dot at the beginning of the line indicates 100 mm Hg and two dots 140 mm Hg. This convention is used in all figures in this paper.

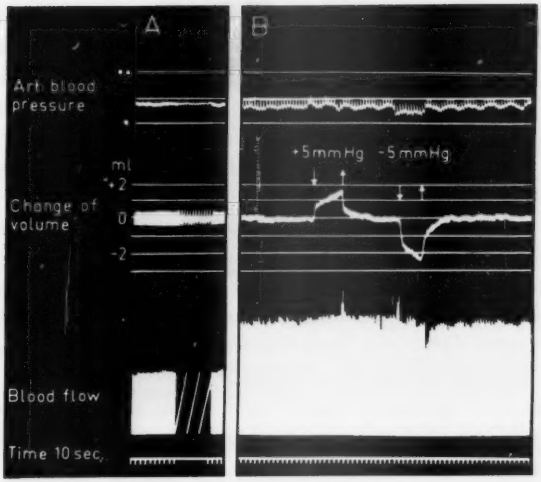

Fig. 2. Cat 3.4 kg. Chloralose-uretane. *A*. Arterial blood pressure, volume and blood flow of the cat's hind parts recorded 'at rest' and at 'isovolumetric state'. Calibration of blood pressure: one dot = 100 mg Hg, two dots = 140 mm Hg, used in this and following figures. *B*. During 'isovolumetric state' venous outflow pressure increased and decreased so as to induce changes in capillary hydrostatic pressure of ± 5 mm Hg. The initial rapid changes in volume reflect effects of altered distension of the capacitance vessels. The second, slower and continuous changes in volume are due to transcapillary filtration efflux and influx respectively. Outward filtration rate in this experiment approximately 0.025 and inward filtration rate approximately 0.03 ml/min/mm Hg/100 g tissue. Blood flow insignificantly influenced by these procedures.

appeared, though in the opposite direction. Blood flow was, however, often not altered significantly by such minor changes in venous outflow pressure. The initial and rapid change in volume is interpreted as being due to altered degree of distension of the vessels, mainly the thin-walled veins, resulting in a slightly increased or decreased blood content in these vessels. The continuous and slow deflection of the volume curve reflects in all probability the effects of a change in hydrostatic capillary pressure and therefore in net filtration exchange across the capillary walls. Essentially the same phenomena have previously been demonstrated with an equivalent technique and discussed at length by PAPPENHEIMER and SOTO-RIVERA (1948) in their extensive studies on capillary exchange. — The change in capillary hydrostatic pressure induced by the experimental steps as shown in Fig. 2 *B*, would, owing to the relation between pre- and postcapillary resistances at normal vascular tone, approximately comprise 75—80 per cent of the experimentally added increase in venous outflow pressure (PAPPENHEIMER and SOTO-RIVERA 1948). Once

this value of the induced capillary pressure change and the magnitude of the described continuous and slow volume shift were known, the filtration rate in the region could be expressed in absolute values, correlated to the pressure change in mm Hg, to unit time and to the tissue mass. The 'filtration coefficient' thus calculated by the present technique generally comprised about 0.02—0.03 ml/mm Hg/min/100 g tissue, a figure which roughly corresponds to the data on filtration rate in skeletal muscle presented by PAPPENHEIMER and SOTO-RIVERA (1948). In some experiments a filtration coefficient as high as 0.04 ml/mm Hg/min/100 g tissue was encountered, but it should be remembered that this preparation, in addition to skeletal muscle, also included skin, where the filtration rate might be higher. As pointed out by PAPPENHEIMER (1953) the filtration coefficient can vary considerably in different tissues. Further, the magnitude of the coefficient must also depend on the number of capillaries open to flow at the moment of measurement. The more capillaries that are open, the higher the filtration coefficient, other factors being unchanged.

As a comparison with the effects induced by changing the venous outflow pressure, Fig. 3 illustrates the typical response to electrical stimulation of the peripheral ends of the two abdominal sympathetic chains at 2 impulses/sec, and at such a voltage and pulse duration that all fibres were activated (see p. 18). Blood flow, reflecting the effects on the resistance vessels, decreased rapidly, and the maximum vasoconstrictor response obtainable at this stimulation rate, attained within 30 sec, persisted for the remaining period of stimulation. When the stimulation was interrupted the vessels again dilated rapidly, and reached the pre-stimulatory level of tone after a short period of slight 'reactive hyperaemia'. The increase in peripheral resistance here obtained in response to the sympathetic stimulation is calculated to comprise about 130 per cent. — The volume of the hind parts of the cat decreased simultaneously with the blood flow decrease at stimulation. A detailed analysis reveals two different characteristics of the slope of the volume curve (indicated by the two dashed lines in the second tracing). There was an initial and rapid decrease in volume within the first 30 sec, thus synchronous with the rapid decrease in flow (indicated by the vertical lines in the second tracing). This was followed by a rather distinct bend in the curve. After this bend there was a definitely slower and continuous decrease in volume during the remaining period of stimulation, despite the fact that blood flow during the same period remained stable. — When the sympathetic stimulation was interrupted there was first a phase of rapid increase in volume, which was completed at the same moment as the resistance vessels had dilated, to judge from blood flow. This was followed again by a sharp bend in the volume

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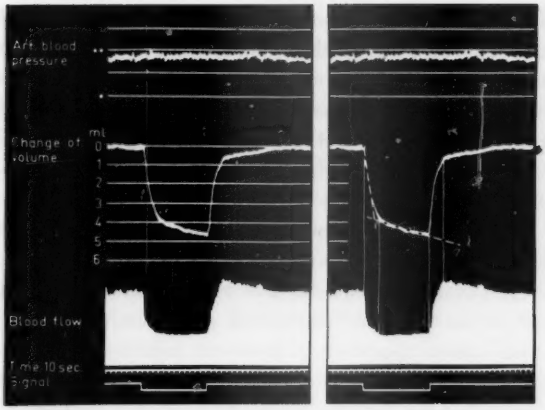

Fig. 3. Cat 2.9 kg. Chloralose-uretane. Effects on volume and blood flow of the cat's hind parts at constant inflow and outflow pressures during maximal stimulation of the lumbar sympathetic vasoconstrictor nerves at a rate of 2 impulses/sec (signal). The initial and rapid decrease in volume represents an expulsion of blood from the capacitance vessels, while the subsequent slow and continuous decrease reflects transcapillary influx of extravascular fluid secondary to hydrostatic capillary pressure fall. The effect on the resistance vessels (see blood flow) is synchronous with that on the capacitance vessels (indicated by vertical lines in second tracing. This tracing is identical with the first one). The vascular responses reversible after interruption of stimulation.

curve and a definitely slower increase in volume until, after a few minutes, the isovolumetric level was again reached. The magnitude of the rapid decrease in volume during early stimulation equalled that of the rapid gain when the stimulation was ended. Also the two slow phases of change in volume were of the same order of magnitude.

To analyse the effects of sympathetic stimulation on the capacitance vessels more selectively, under circumstances where interference of, for instance, fluctuating flow and inflow pressure was excluded, the following experiment was undertaken. Occluding clamps were applied at exactly the same moment, one on the abdominal aorta and the other on the distal part of the abdominal caval vein, so that inflow and outflow from the studied region were stopped completely. 30 sec later, when a pressure equilibration within the vascular bed of the hind parts must have occurred, the clamp on the caval vein was removed. No venous outflow appeared as a result of this action. On the contrary, blood stored in the outflow cannula and tubing slowly passed in a retrograde direction through obviously not completely sufficient venous valves into the hind parts, the volume of which increased to a slight extent simultaneously, revealing the ischaemic dilatation of the

vascular bed. — If exactly the same procedures were repeated, only with the difference that, some 30 sec after the application of the two occluding clamps, the sympathetic vasoconstrictor nerves of the hind parts of the cat were stimulated continuously, a rapid venous *outflow* now appeared and the tissue volume decreased at the removal of the clamp on the caval vein. These changes were both completed within less than 20 sec. This experiment reveals a neurogenically induced increase of tone in the capacitance vessels during stimulation, leading to a raised pressure within the occluded vascular bed, which pushes out blood as soon as the venous outlet is opened. In fact, it implies first an 'isometric' contraction of the capacitance vessels, then suddenly changed to an 'isotonic' contraction when the caval vein is opened. The sympathetic stimulation did not, however, induce any change in volume as long as the two clamps occluded both aortic inflow and caval outflow. Nor was the volume changed by the occlusion as such. This showed that no vascular collaterals were left between the hind parts and the main part of the animal in this preparation.

There can thus be little doubt that the initial and rapid phase of the volume decrease, demonstrated in Fig. 3, was mainly due to a constriction of the capacitance vessels, which squeezed out part of their blood content. The slow and continuous reduction of tissue volume shown in Fig. 3 is interpreted as an effect of a decreased hydrostatic capillary pressure, caused by a relatively more pronounced constriction of the precapillary than of the postcapillary resistance vessels. Proofs of this interpretation will be given below (see p. 28—30), but some general considerations of this problem may be stated already here to make the analysis of the volume curve of Fig. 3 more complete in this connection. If, at a given arterio-venous pressure difference, the precapillary resistance is relatively more increased than the postcapillary resistance, the profile of the pressure fall curve along the various sections of the vascular bed will be changed in such a way that capillary blood pressure is decreased. This fact can easily be demonstrated in hydrodynamic model experiments or by electrical analogues. Such a decrease in capillary hydrostatic pressure would result in a slow absorption of extravascular fluid from the tissues into the circulatory system. Proofs that such an absorption does take place are given below, see p. 28—30. The 'mobilized' tissue fluid would then be drained together with the perfusing blood *via* the venous channels, resulting in a slow, continuous reduction of tissue volume and a slight 'dilution' of the passing blood. — When the sympathetic stimulation that induced these vascular effects was ended, the resistance and the capacitance vessels again dilated (see Fig. 3), and capillary blood pressure should then be restored to the previous level, or probably raised even above that value, during the period

of reactive hyperaemia when the resistance vessels, particularly the precapillary ones, were temporarily relaxed somewhat beyond their pre-stimulatory tone level (see below). Further, as the hydrostatic pressure of the tissue must have been somewhat decreased, and tissue colloid osmotic pressure slightly increased, owing to the drainage of extravascular fluid during the stimulation, forces should be created that tend to filter fluid back to the tissues. Such factors probably explain the fact that the isovolumetric state was reached rather quickly after stimulation ceased. In some experiments, however, particularly where no significant post-stimulatory reactive hyperaemia was seen, the pre-stimulatory volume level was not fully reached after stimulation ended. The volume then remained constant at a new level, slightly below the initial one. The compensation for tissue fluid loss during stimulation was thus not always complete.

The above-mentioned interpretation of the recorded volume changes at sympathetic stimulation needs, however, additional experimental data and comments to be clarified. The mobilization of blood from the capacitance vessels at stimulation can *a priori* be the result of two different phenomena for the following reasons: besides having an effect on the capillary pressure, a constriction of predominantly the precapillary section of the resistance vessels can be expected to cause a reduction of the hydrostatic distending pressure within the veins also — the main part of the capacitance section — even when arterial inflow pressure and venous outflow pressure are kept constant. This can also be demonstrated as occurring in hydrodynamic model experiments. Such a decrease in the mean venous pressure will result in a certain elastic recoil within these highly distensible vessels and thus induce a 'mobilization' of part of their blood volume. This process will here be called a 'passive' one as contrasted with the 'active' mobilization of blood induced by the activation of the smooth muscle of the capacitance vessels. Although such a passive phenomenon would be of importance for the net functional response to sympathetic stimulation, in many circumstances the 'passive' and 'active' phenomena take opposite directions as, for instance, in the legs on change from supine to erect position. It is therefore of interest to differentiate quantitatively between this passive event and the active constriction of the capacitance vessels that forms the more direct result of sympathetic stimulation. For that purpose a drastic change in intravascular pressure was produced by completely occluding the abdominal aorta, thus reducing the arterial pressure in the studied vascular bed to the level of the venous outflow pressure (see Fig. 4, arrow *A*). Superimposed on this procedure an electrical stimulation of the sympathetic nerves of the hind parts was performed (arrow *B*). While at arterial occlusion an almost immediate reduction of blood flow

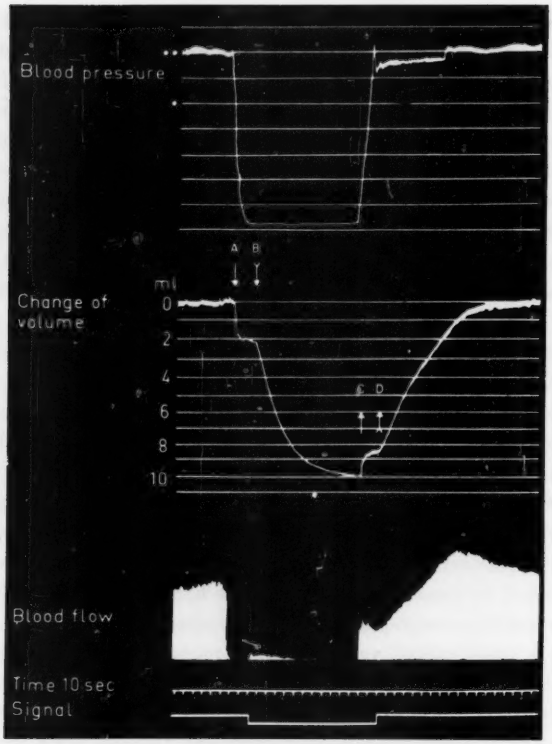

Fig. 4. Cat 3.0 kg. Chloralose-uretane. Arrow *A*. Intravascular pressure reduced to the level of venous outflow pressure by clamping the abdominal aorta, resulting in cessation of blood flow and a 'tissue' volume decrease of about 2 ml ('passive-elastic recoil' of capacitance vessels). At arrow *B*, superimposed on the aortic clamping, lumbar sympathetic vasoconstrictor fibres stimulated at 6 impulses/sec, inducing a tissue volume decrease of about 8 ml which equalled the amount of reappearing blood outflow (effect of active constriction of the capacitance vessels). At *C*, aortic clamp removed and at *D* the sympathetic stimulation turned off. Signal = stimulation period.

to zero naturally occurred, there was a rather limited rapid decrease in volume concomitantly, comprising only some 2 ml, due to the passive elastic recoil of the capacitance vessels. This was again followed by a much slower but steady volume decrease (similar to the slow and continuous phase of volume decrease seen in Fig. 3). This last, very slow decline would go on for about a minute but eventually level off gradually, giving no further change of tissue volume if no other experimental step was introduced. — At

the subsequent sympathetic nerve stimulation at arrow *B*, there was, however, an additional extensive and rapid decrease in tissue volume amounting to somewhat more than 7 ml. Under these experimental conditions of constant intravascular pressure this volume decrease must be due to an *active* constriction of the capacitance vessels. There now followed again another slow phase of volume reduction, comprising somewhat less than 1 ml, and showing the same characteristics with regard to the slope as the above-mentioned *slow* volume decline at arterial occlusion. — A small venous outflow of blood reappeared at the beginning of the stimulation and, collected in a test tube during the period between *B* and *C* (see the figure), it was demonstrated to amount to exactly 8 ml, thus equalling the simultaneously recorded decrease in tissue volume. The recorded change in volume at stimulation is thus a correct indicator of the amount of fluid that is mobilized from the vascular bed during the stimulation period. — The experimental steps were then reversed. The occluding clamp on the aorta was first removed, thus restoring the perfusion pressure to normal level (arrow C) and resulting in a certain augmentation of blood flow and a volume increase corresponding roughly to the previous 'passive' decrease. Only when the stimulation ceased (arrow *D*) did the blood flow reach its initial level, but it rapidly surpassed this to form a reactive hyperaemia. Simultaneously with these latter flow changes there was an increase in tissue volume to the initial level, but it should be noted that no more significant 'reactive dilatation' of the capacitance vessels was obtained. — It should be stressed that the 'passive' volume decrease, here demonstrated at the elimination of arterial inflow pressure, must be especially large, as such a drastic decrease in mean intravascular pressure as that obtained on complete arterial occlusion will probably never occur even at maximal sympathetic discharge in the intact organism. The experiment described above thus reveals the extent of the maximum passive elastic recoil obtainable in the studied vascular bed under the prevailing conditions, by way of decreases of the distending pressure. The 'passive' mobilization of blood secondary to *sympathetic stimulation*, when the intravascular pressure is far less reduced, must then be considerably smaller. It can therefore under the present circumstances be largely neglected from a quantitative point of view, as compared with the effects obtained by the 'active' smooth muscle constriction. It might also be remarked that, from a functional point of view, the question to what extent the 'passive' or 'active' components separately contribute to the induced blood mobilization, should in most circumstances be more of secondary interest, as both phenomena are after all induced by the same stimulus, the sympathetic activation. However, the 'passive' component — the elastic recoil of the capacitance vessels — is mainly a

consequence of constriction of the resistance vessels, while the 'active' component is due to activation of the smooth muscles of the capacitance vessels. Further, there are, as has been mentioned, situations when such 'active' and 'passive' factors have opposite directions. The influence of sympathetic constrictor fibre discharge on the passive elastic recoil in the vascular bed will therefore be investigated in more detail in a subsequent study. — It should be emphasized that the volume shifts described, obtained at sympathetic stimulation, were by no means influenced by any concomitant activation of the skeletal muscles of the hind parts. Such an unexpected contraction of this type of muscle was namely never observed in these experiments; further a complete curarization of the cat did not change the recorded responses significantly.

From the above-mentioned considerations it seems evident that the steep slope of the volume recording at sympathetic stimulation, as illustrated in Fig. 3, can be safely regarded as a fairly accurate indicator of an actively induced decrease in blood content of the vascular region studied, implying a rapid mobilization of blood, caused by vasoconstriction within the capacitance section of the vascular bed.

If, as has been assumed, the slow and continuous decline in the recorded tissue volume that appears after the initial rapid phase of volume decrease at sympathetic stimulation (Fig. 3), is caused by a decrease in mean capillary pressure, it should be possible to counterbalance this slow decrease by slightly increasing the venous outflow pressure, as the capillary pressure would then again rise. Fig. 5 illustrates the typical effect of a suddenly increased venous outflow pressure, in this case increased by about 7 mm Hg, superimposed on the fully developed constrictor response at sympathetic stimulation. The slower phase of volume decline was then suddenly stopped and the curve first rose slightly but rapidly, after which it levelled off horizontally. If, in this experiment, the applied venous pressure was less or greater, there appeared respectively a slight downward or upward continuous deflection. If, on the other hand, venous outflow pressure was increased during the *initial, rapid* shift in volume caused by sympathetic stimulation, it was not possible to counteract this phase of volume reduction, except for an occasional short delay for a few seconds. It therefore seems likely that the second slower volume decrease recorded during sympathetic stimulation is related to a capillary pressure drop resulting in absorption of extravascular fluid.

If extravascular fluid is absorbed and mixed with the venous blood its colloid osmotic pressure should decrease slightly. In order to investigate the protein content in the plasma, venous blood drained from the hind parts was collected in small samples at short intervals before, during and after sympathe-

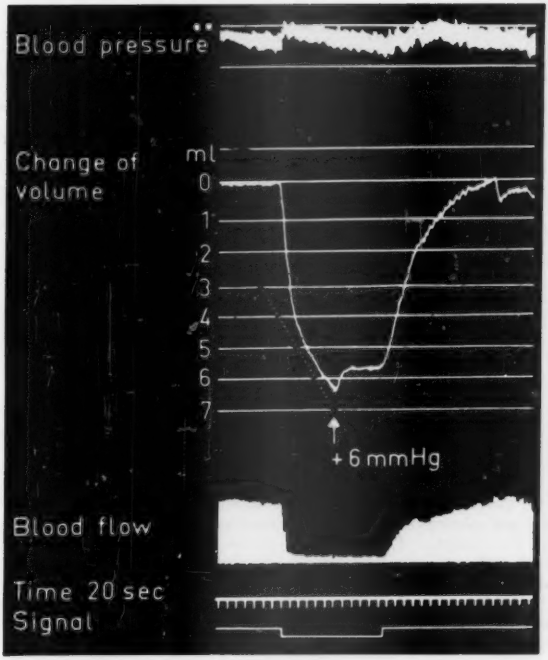

Fig. 5. Cat 3.0 kg. Chloralose-uretane. Sympathetic vasoconstrictor fibres stimulated, 6 impulses/sec (signal). After the initial and rapid decrease in volume, due to constriction of the capacitance vessels, a slower decrease appeared, interpreted as being due to transcapillary tissue fluid absorption secondary to capillary pressure fall. The slope of this phase indicated by the dotted line. The induced capillary pressure fall calculated to comprise roughly 6 mm Hg. At the arrow, venous outflow pressure raised so as to induce an increase in capillary pressure of about 6 mm Hg. By this procedure the absorption process was counterbalanced, as revealed by the 'isovolumetric state' obtained.

tic stimulation, and later on tested on plasma protein content according to the Kjeldahl method. Such experiments were performed on 8 cats. It could be demonstrated in these experiments that the protein content in the drained venous plasma, representing the colloid osmotic pressure, was constant before and during the initial rapid phase of blood mobilization at sympathetic stimulation, but that it decreased significantly (often up to 30-35 per cent) in blood sampled during the slow and continuous, late phase of volume reduction. Fig. 6 illustrates such an experiment with the values of percentage change in protein content of the plasma indicated, both as computed on the

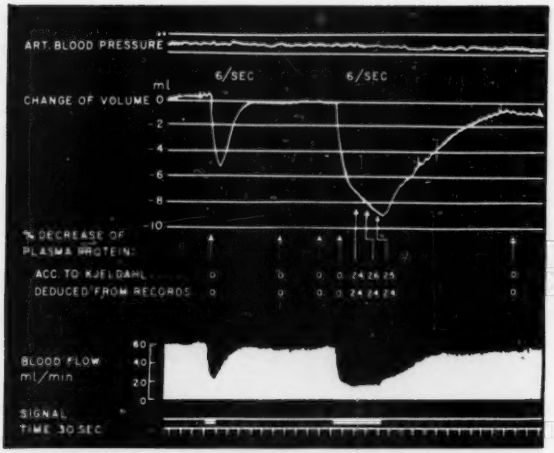

Fig. 6. Lumbar symp. chains stimulated at 6 imp./sec first for a short period and then for such a long period that the slow and continuous phase of volume decrease due to extravascular fluid absorption appeared. Samples of the drained blood withdrawn at short intervals for analysis of plasma protein content. During the slow and continuous volume decrease, plasma protein decreased markedly owing to the dilution with extravascular fluid. During the initial rapid volume decrease due to capacitance vessel constriction, no change in protein was generally detectable. Approximate values for protein dilution, based on actual plasma flow and transcapillary influx, conformed well to the estimates by the Kjeldahl analysis.

basis of the recorded rate of plasma flow and transcapillary inflow, and as verified chemically in representative blood samples by the Kjeldahl protein analysis.[1]) This close resemblance between the values computed from the records and those obtained by the chemical analysis of the changes in plasma protein during sympathetic stimulation was a constant finding in all these experiments.

The experimental evidence described therefore strongly suggests that the slow and continuous volume shift during sympathetic stimulation is due to a decreased hydrostatic capillary pressure, in turn causing an absorption of extravascular fluid from the tissues into the circulatory system. This phenomenon can be reasonably explained only on the basis of a relatively greater increase of the precapillary than of the postcapillary resistance in response to

[1]) I am indebted to Dr. Björn Isaksson, Dept. of Clinical Chemistry, Sahlgren's Hospital, Göteborg, Sweden, for performing the Kjeldahl analyses.

sympathetic stimulation. — It is likely that this absorption process is initiated as soon as the precapillary resistance vessels start to constrict, thus already at the onset of the stimulation. This means that a certain component of the initial and rapid volume decrease at stimulation should be due to such an absorption. As, however, this absorption is usually a very slow phenomenon in comparison with the effect of the nervous constriction of the capacitance vessels, the amount of absorbed fluid during the period of capacitance vessel constriction, — say the initial 20 sec — is very small. During this short period it was generally not possible to detect any significant change in plasma protein content. To get more correct quantitative data concerning the sympathetic constrictor effects on the capacitance vessels, *i. e.* the mobilized blood amount, a more detailed analysis of the curve was made; two lines were drawn, one along the rapid curve deflection and the other along the continuous absorption slope, and the effect of constriction on the capacitance vessels was then measured only down to the intersect between these two lines (see Fig. 3, second tracing). This correction generally changed the directly recorded constrictor effect of the capacitance vessels very little.

The main purpose of the present investigation is thus to analyse in detail the reaction *per se* of the different consecutive 'series-coupled' sections of the vascular bed, when exposed to the action of a graded uniform sympathetic vasoconstrictor fibre discharge or catechol hormone release (see chapters IV and V). To make this possible it is necessary to study the vascular bed under certain standardized experimental circumstances. From some points of view, this implies rather drastic divergences from the conditions in the intact organism. It is, however, justified to perform such studies, simply because they are a necessary pre-requisite for the full understanding of the still more complex responses to neuro-hormonal influence occurring in the intact organism, where several interfering factors have to be taken into consideration. It must then be discussed to what extent divergences from the conditions in the intact animal, inherent in the present preparations, such as the anaesthesia, may have affected the results. Different anaesthetics were tried, also in different doses, but the results of vasoconstrictor fibre stimulation were essentially the same whether chloralose, chloralose-uretane, uretane or dial was used. It was mainly the dilator response to adrenaline, described in detail in chapter V, that varied to a more significant extent according to the anaesthetic used. Thus under uretane or dial anaesthesia the dilator response was generally more pronounced and could be maintained at higher concentrations of adrenaline than during chloralose anaesthesia. This fact has been pointed out in a previous study (LUNDHOLM 1957), where it was concluded that the dilator effect of adrenaline during uretane anaesthesia

bore greater resemblance to that seen in the intact animal than when chloralose was used.

Artificial respiration was given in about half of the experiments, but this did not affect the results significantly as compared with those obtained in animals which breathed spontaneously. — Skeletal muscle tone was largely abolished in the used preparation by interfering with the somato-motor nerve supply. In a few control experiments these nerves were left intact, but the response to sympathetic stimulation or to catechol amines under such circumstances did not differ significantly from the results reported in this chapter and in chapters IV and V.

Further, the venous outflow pressure from the studied region was kept constant in most experiments, which is hardly the case in the intact organism, though presumably here also the variations are generally quite small. By keeping the venous outflow pressure constant, the mobilized amount of blood was enabled to leave the regional vascular system without any change in resistance to its outflow. However, venous inflow from the studied tissue area to the heart was regulated so as to coincide with the outflow from the hind parts. Further, in some experiments, blood flow was not recorded, so that the caval vein could be left entirely intact. The venous outflow pressure from the vascular bed should here be about the same as in the intact animal, but also under these circumstances, the reactions of the capacitance vessels to sympathetic stimulation were not essentially different from those here presented. In the present experiments the arterial systemic blood pressure was generally but little affected by the changes in regional resistance, as induced by the sympathetic stimulation, except upon splanchnic stimulation, when the adrenal medullary hormones were distributed throughout the cardiovascular system. In experiments where the arterial inflow pressure was not controlled the results were, however, essentially the same as those here described, both with regard to the resistance and capacitance vascular responses and the effects on capillary filtration.

Lastly, in some experiments minor blood losses occurred and had to be substituted by equal amounts of dextrane Tyrode solution. There is no doubt that part of the dextrane escapes from the blood stream in the capillaries. This could often be seen on the records, as the tissue volume increased slightly soon after dextrane administration. However, a new transcapillary equilibrium was generally established within about 5 minutes, to judge from the isovolumetric state attained once more. If therefore dextrane was given, a sufficient time lapse was always allowed so that a transcapillary equilibrium and an isovolumetric state were obtained before new experimental steps were introduced.

It can thus be concluded that, in most respects, the vascular reactions recorded under the prevailing standardized conditions do not seem to differ too much from those occurring in the intact organism. Still, it is evident that care should be taken not to draw over-simplified conclusions from this type of experiment as regards the circulatory control in the intact animal, where the situation is still more complicated.

CHAPTER IV

Effects of graded sympathetic vasoconstrictor fibre stimulation on resistance and capacitance blood vessels

The above-mentioned experimental evidence concerning the potentialities of the method described in differentiating and analysing the haemodynamic reactions of the various consecutive vascular sections was taken as a basis for a more detailed study of the effects of *graded* sympathetic vasoconstrictor fibre stimulation on the resistance and capacitance vessels. Interest was focused on the effects of low frequency stimulations, as other studies indicate that normally vasoconstrictor fibre discharge hardly ever surpasses 8 to 10 impulses/sec and that the tonic, 'resting' discharge is as low as 1 to 2 impulses/sec (see FOLKOW 1952 a, 1956 a). Special attention was paid to some aspects of importance both for the regional vascular bed as such, and for the cardiovascular system as a whole. *Firstly*, the interrelationships of the nervous control of the resistance vessels, as contrasted with that of the capacitance vessels, were studied; *secondly*, an attempt was made to analyse the vasoconstrictor fibre influence on the ratio between the pre- and postcapillary resistances, with special regard to its influence on filtration across the capillary walls. It then proved possible to evaluate to what extent the vasoconstrictor fibre control allows not only for a 'mobilization' of blood, but also of a fraction of the extravascular fluid.

1. Effects on resistance vessels as compared with effects on capacitance vessels

a. Results. Fig. 7 demonstrates the typical effects obtained in an experiment in which the vasoconstrictor fibres of the skin-muscle region of the cat's hind parts were stimulated for periods of about 1 min and at stimulation frequencies increased step by step (for technical details, see chapter II). The frequencies studied ranged between 0.25—32 impulses/sec and those tested in each experiment as a matter of routine are indicated by numerals along the abscissa in the diagram in Fig. 8 (except 32/sec). As illustrated by the blood flow records in Fig. 7, the constriction of the resistance vessels was more pronounced the more the rate of the stimulation was increased. A

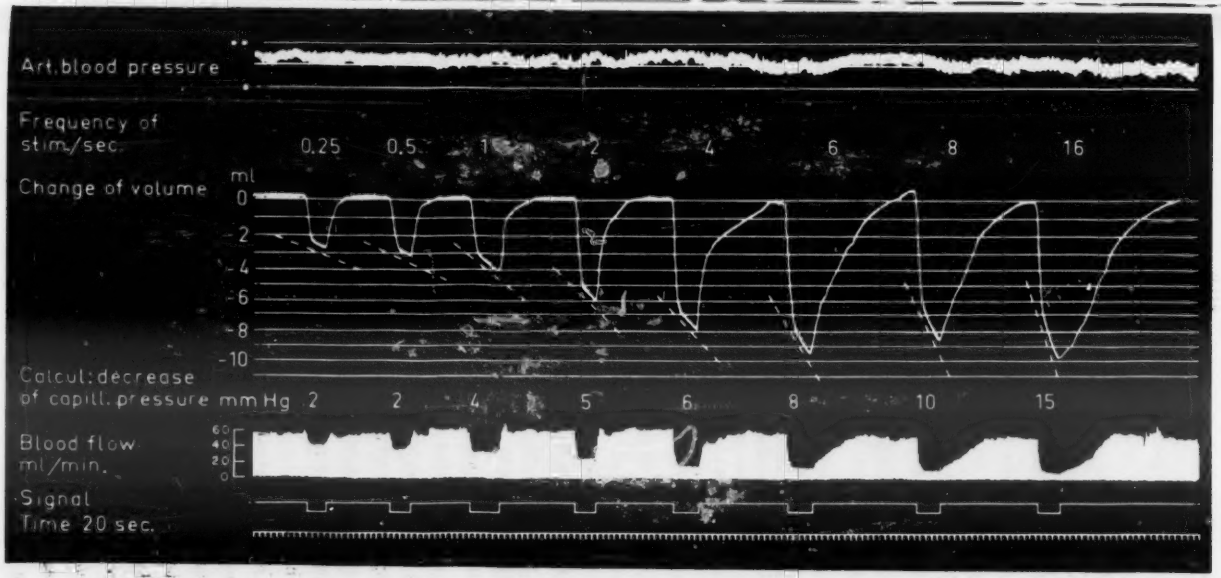

Fig. 7. Cat 2.9 kg. Chloralose-uretane. Effects on resistance and capacitance vessels and net transcapillary fluid shift during maximal lumbar vasoconstrictor fibre stimulation at different frequencies, as indicated. Changes in blood flow reflect effects on resistance vessels (inflow and outflow pressures kept constant). The initial and rapid decreases in volume reflect effects on capacitance vessels and the subsequent slower and continuous decreases in volume (slopes indicated by dashed lines), transcapillary influx of extravascular fluid. The reductions in mean hydrostatic capillary pressure calculated in approximate figures. The maximum response of capacitance vessels reached at about 6 impulses/sec but in resistance vessels first at 16 impulses/sec. Rates of stimulation exceeding 16/sec did not further augment the vascular responses. Total regional blood volume contained at 'basal tone' in the vascular bed studied comprised about 20 ml.

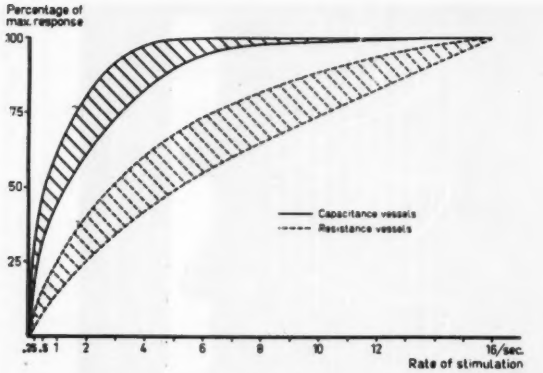

Fig. 8. Frequency-response curves deduced for resistance vessels (dashed lines) and capacitance vessels (continuous lines) in skin-muscle region of cat. Effects of lumbar vasoconstrictor fibre stimulation calculated in percentage of the maximum responses obtainable in the two vascular sections. These curves based on results obtained in 40 experimental animals, shaded areas indicating all individual variations. Note that the curve for the capacitance vessels is placed to the left implying *relatively* more pronounced effects in this section in the low frequency range as compared with those of the resistance vessels.

maximal response was obtained around 16 impulses/sec, although about 80 per cent of maximum was already reached at the rate of 8/sec.

The constrictor responses of the capacitance vessels were also related quantitatively to the frequency of sympathetic stimulation. As previously mentioned, the constrictor responses of the capacitance vessels were represented by the initial and rapid decline of the volume curve. A maximal response to stimulation was in this experiment obtained already at 6 impulses/sec. The constrictor response already reached in fact about 80 per cent of the maximal one at 2—4 impulses/sec. A definite vasoconstrictor effect was obtained in both vascular sections at as low a stimulation frequency as one impulse each fourth sec.

The diagram in Fig. 8 illustrates the functional response of the resistance vessels to sympathetic stimulation — represented by the calculated increase in peripheral resistance — and the functional response of the capacitance vessels — represented by the amounts of blood mobilized from the hind parts of the cat. The degree of vasoconstriction within the two sections is here expressed as a percentage of the respective maximum responses obtainable — *i. e.* given in *relative* figures — and plotted against the stimulation frequencies. This diagram is based on 40 experiments which were entirely satisfactory from a technical point of view. The range of individual varia-

tions is shown by the shaded areas. Continuous lines represent the reactions of the capacitance vessels and dashed lines those of the resistance vessels. – When the haemodynamic responses of the two consecutive vascular sections of the combined skin-muscle region are compared in this way, it becomes evident that the stimulation frequency-response curve of the capacitance vessels, in its entire length, is placed to the left of that of the resistance vessels. This implies that the maximum response is reached at a lower sympathetic discharge rate in the capacitance vessels than in the resistance vessels and that still lower stimulation frequencies will always induce proportionally more pronounced changes within the capacitance section when related to the respective maximal responses. — Frequency-response curves deduced for the resistance and capacitance vessels of the 'isolated' muscle region showed in principle the same characteristics as those of the combined skin-muscle region. Thus the values along the curves, deduced from the vascular effects in the muscle region, all fell within the limits indicated in Fig. 8.

So far the vascular responses to sympathetic stimulation have been expressed only as *percentage* changes, in order to compare more easily the slope characteristics of the frequency-response curves in the resistance and the capacitance vessels. By this comparison certain fundamental aspects of the nervous control of the two vascular sections were elucidated, and the differences hereby revealed will be further commented on below. — It is, of course, also of great interest to compare the *'absolute'* changes of smooth muscle tone in the resistance vessels — in terms of increase of resistance — with those of the capacitance vessels — in terms of the fraction of their blood content expelled. Moreover, it would be of importance to get some idea of the actual changes in mean internal radius which take place within the mentioned vascular sections. From many points of view such data are more relevant for the right appreciation of the range of sympathetic vasoconstrictor fibre control in the adjustment of resistance to flow and blood distribution.

With regard to the resistance vessels, such information is easily obtained by calculating the increase of flow resistance at any given stimulation frequency, as compared with the resistance existing when the vessels are not exposed to any vasoconstrictor fibre activity, but only exhibiting their 'basal tone'. At maximum effective stimulation the regional resistance to flow in the hind parts generally rose 5—8 times above that at 'basal tone'. The induced increases in resistance at the different rates of stimulation expressed in relative peripheral resistance units are indicated in Fig. 19, curve A_r. – It is, however, somewhat more difficult to get similar information concerning the capacitance vessels. For such purposes it is necessary to know the regional blood volume when the vessels of the hind parts are unexposed

to any sympathetic activity and when a reasonably stable 'basal tone' of the capacitance vessels is maintained. The measurement of the contained 'basal' blood volume must then be made after the inflow pressure and outflow pressure are so adjusted as to maintain the regional 'isovolumetric' state and the blood flow in steady equilibrium with the resting metabolism of the tissues in the hind parts. First under such circumstances is there a reasonable 'baseline' for a more exact calculation of the changes of tone in the capacitance vessels that are induced by graded sympathetic stimulation.

The isotope technique[1]), previously described, revealed that under these 'basal', steady state conditions the amount of blood present in the cat's hind parts was remarkably constant in different animals, if only correlated to the weight of the studied tissue mass. In cats of a total body weight of 3 kg the 'basal' blood volume in the hind parts comprised about 20 ml, or some 2.5—3 ml of blood per 100 g tissue, a finding which corresponds well to similar measurements of the blood content in the hind limbs of cats (see PAPPENHEIMER 1953) and in hind limbs of dogs (SHADLE, ZUKOF and DIANA 1958). Similar values for the regional blood content were obtained in experiments in which the 'Hb-dilution method' for blood volume determination was utilized (see p. 17).

Thus the problem was to determine the fraction of this 'basal' blood volume of the hind parts that under the prevailing circumstances could be expelled by sympathetic activation. Fig. 9, representing a typical experiment, illustrates the reduction in the blood volume of the hind parts, induced when the vasoconstrictor fibres were stimulated at various rates. Both absolute values in terms of ml of blood volume mobilized and percentage values of the initial blood content are indicated. It can be seen that in this experiment, as in most others, up to approximately 35 per cent of the total regional blood content could be expelled; in a few experiments a mobilization of as much as 40 or even 50 per cent occurred. At the most effective sympathetic stimulation the regional blood volume was thus generally decreased to about 2/3 of its initial volume. This figure should be contrasted with the average maximal increase of regional flow resistance on sympathetic stimulation, which was generally from five- to eightfold.

On the assumption that the great majority of the smooth muscles both of the resistance and the capacitance vessels are arranged circularly in the vascular walls — implying no essential shift in tube length but only in radius — the induced decrease in percentage of the internal radius of an 'average'

[1]) I am most obliged to Dr LEIF HALLBERG, Haematological Laboratory, Medical Clinic II, Sahlgren's Hospital, Göteborg, Sweden, for invaluable help with the blood volume determinations.

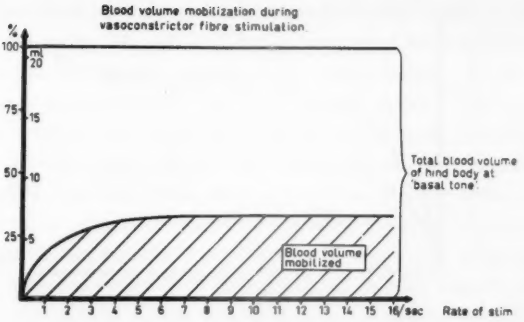

Fig. 9. Diagram illustrating the amounts of blood 'mobilized' from capacitance vessels in the hind parts of a cat (bodyweight 3 kg) during lumbar vasoconstrictor fibre stimulation at various rates, in relation to the total regional blood volume contained at 'basal tone'. Up to about 1/3 of the regional blood volume can be expelled and already at as low a stimulation rate as 6—8 impulses/sec.

resistance and capacitance vessel can be approximately computed. According to the Poiseulle law, the flow resistance is inversely proportional to the fourth power of the internal radius. If it is assumed that apparent viscosity is not too much changed during smooth muscle constriction, the decrease in percentage of internal radius in the 'average' resistance vessel can be deduced *approximately*. There is in fact experimental evidence suggesting that viscosity is rather lowered than raised when the bore of capillary tubes is narrowed (see BAYLISS 1952, p. 369, HAYNES 1956, cf. also LEVY 1956). However, at constriction of very narrow tubes, obstruction of their lumina by way of blood cells must be a factor to take into account in this connection (see below). — The decrease in percentage of internal radius of an 'average' capacitance vessel can be approximately calculated if the capacitance section is considered a thin-walled cylindrical tube of constant length. The decrease of internal radius is then proportional to the square root of the decrease in its blood volume.

Such admittedly rough figures are nevertheless of interest as in some respects they are more directly compatible than are flow resistance and vascular volume. Their interrelationships are illustrated in the diagram of Fig. 10 and are here calculated from typical responses obtained in a combined skin-muscle region. It can be seen that the maximal decrease of internal radius in an 'average' resistance vessel is far more pronounced than that in an 'average' capacitance vessel (about 35 and 20 per cent, respectively), a fact that will be discussed below.

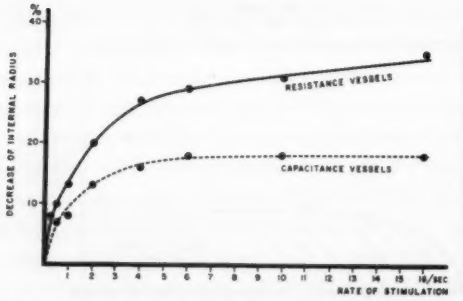

Fig. 10. Calculated luminal reduction in resistance and capacitance vessels during vasoconstrictor fibre stimulation. For details see text.

Fig. 11 shows the average amounts of blood mobilized per 100 g of tissue on sympathetic stimulation in the combined skin-muscle region (curve *A*, mean of 5 experiments), as contrasted with the amounts of blood mobilized in the 'isolated' muscle region (curve *B*, mean of 5 experiments). It can be seen that the amount expelled from the vascular bed in the isolated muscle region is slightly less per unit tissue weight than that in the skin-muscle region. This was a constant finding in all the experiments. The skin-muscle preparation consisted of about 20 per cent skin tissue. From such data it

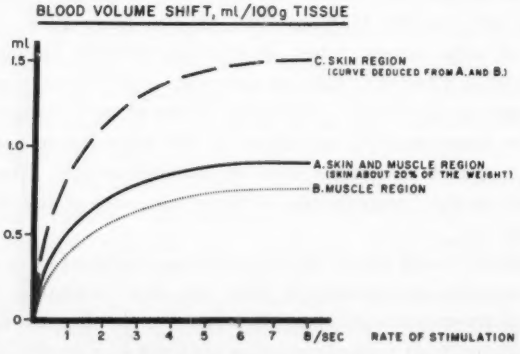

Fig. 11. Diagram illustrating the amounts of blood per 100 g tissue 'mobilized' from a combined skin-muscle region (*A*) and from an isolated muscle region (*B*) in the cat during graded vasoconstrictor fibre stimulation (each curve mean of 5 experiments). Total blood content at 'basal tone' in a skin-muscle region comprises about 2.5—3 ml/100 g tissue, that of a muscle region slightly less. Curve *C*, representing an isolated skin region, is *deduced* from the data in curves *A* and *B*.

could then be deduced that the blood mobilization from an isolated skin region might be up to 100 per cent larger than that from an isolated muscle region, when the values are calculated by tissue weight. This difference is probably mainly related to unequal 'basal blood capacity' in the two tissues, as the blood content per 100 g of tissue in the isolated muscle region was found to be less than that in the combined skin-muscle region. It should then be recalled that the 'basal tone', maintained after acute sympathetic decentralization, is more pronounced in a muscle region than in a skin region, at least as regards the resistance vessels (see LÖFVING and MELLANDER 1956). It is further not impossible that the extent of smooth muscle shortening is slightly more pronounced during constriction in cutaneous capacitance vessels than in muscular capacitance vessels. Experiments on a pure skin region have, however ,to be performed before this question can be definitely settled.

b. Comments. The present experiments have shown on the one hand that the frequency-response curve of the capacitance vessels is placed to the left of that of the resistance vessels, implying that the capacitance vessels in the low frequency range are relatively more extensively affected by sympathetic discharge. On the other hand, the maximum percentage decrease of internal radius in an 'average' resistance vessel under sympathetic stimulation seems to be much more pronounced than that of an 'average' capacitance vessel. These findings may at first sight seem puzzling and require some additional comments.

It will first be appropriate to discuss whether these differences might be due to a different *sensitivity* of the smooth muscles of the resistance and the capacitance vessels to the adrenergic transmitter substance, alternatively to a more extensive difference in the number of constrictor fibres supplying them. In the latter case a difference in local concentration of the transmitter substance between the two vascular sections should be obtained at any given frequency of stimulation. It might be expected that effector cells with a more abundant constrictor fibre supply or with a greater sensitivity towards the transmitter should give 'threshold' responses at definitely lower frequencies of sympathetic discharge or at lower concentrations of noradrenaline in infusion experiments. However, when the sympathetic nerves were activated at very low frequencies of stimulation, the resistance and the capacitance sections always showed their first noticeable constrictor responses at essentially the same 'threshold' frequency. Similarly, there was no difference between the two vascular sections with regard to the 'threshold' dose of intra-arterially infused noradrenaline. Numerous such infusion experiments were performed in the investigation described in chapter V. It seems therefore less likely that the observed, rather marked differences in frequency-response

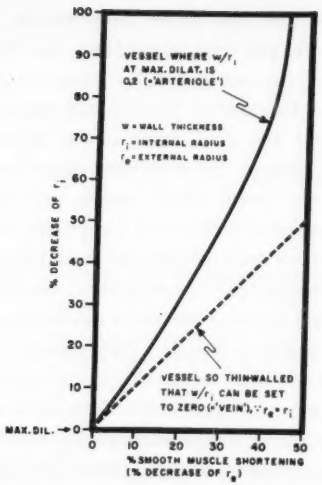
VESSEL WHERE w/r_i AT MAX. DILAT. IS 0.2 (='ARTERIOLE')
w = WALL THICKNESS
r_i = INTERNAL RADIUS
r_e = EXTERNAL RADIUS
VESSEL SO THINWALLED THAT w/r_i CAN BE SET TO ZERO (='VEIN'), ∴ r_e = r_i
% DECREASE OF r_i
MAX. DIL.
% SMOOTH MUSCLE SHORTENING (% DECREASE OF r_e)

Fig. 12. Diagram illustrating the influence of various wall/lumen ratios on the luminal reduction in response to smooth muscle contraction. The 'line of force' for the smooth muscle contraction is in this example assumed to be situated close to the external circumference of the vessel. For details see text.

characteristics are secondary to a difference in effector sensitivity to the adrenergic transmitter or to any more significant difference in the number of constrictor fibres in the resistance and the capacitance vessels.

There is, however, another factor to be taken into consideration, one which necessarily must affect the vascular responses in the observed direction. For purely physical reasons, differences in wall/lumen ratio between the two vascular sections can be expected to influence the functional response, with regard to the extent of luminal decrease obtained by a given degree of smooth muscle shortening. The higher the wall/lumen ratio is — *i. e.* the bigger the wall mass situated inside the 'line of force' of smooth muscle shortening in a 'unit' vessel — the more pronounced the luminal narrowing will become per unit length of smooth muscle shortening (for details see FOLKOW 1956 b, FOLKOW, GRIMBY and THULESIUS 1958). This is so because of the gradually increasing protrusion into the lumen of the inner wall layers, consequent on the smooth muscle shortening. It is in this connection of particular interest that that this structurally based intensification of the luminal reduction must become more and more marked the more the smooth muscles contract. The importance of this physical phenomenon for the resulting luminal reduction in vessels with different cross-sectional architecture is illustrated in principle in

Fig. 12. The solid curve is deduced from the calculated luminal decreases in a vessel supposed to have a rather high wall/lumen ratio (0.2) at maximal dilatation, while the dashed curve represents a vessel where the wall/lumen ratio at maximal dilatation is so small that for practical purposes it can be set at zero. Of course these figures of wall/lumen ratios at maximal dilatation are arbitrary, but they may in fact rather closely reflect the actual conditions found in an arteriole and a vein respectively. As is clear from this diagram, in vessels with relatively high wall/lumen ratios, like arterial vessels, the inner radius can be expected to decrease more strikingly than does the length of their contractile vascular elements, when they contract. Especially when the contractile elements are initially already somewhat contracted, minute *additional* shortenings will lead to unproportionally strong luminal reductions. In thin-walled vessels, like veins, on the other hand, the luminal reduction is more directly proportional to the degree of smooth muscle shortening. This suggests that for one and the same extent of smooth muscle shortening in arterial and venous vessels, the luminal reduction will always be more pronounced in the arterial vessels, as the structural 'potentiation' of the luminal decrease inherent in the bigger wall/lumen ratio of these vessels must always add to the luminal decrease directly caused by smooth muscle shortening. It should be recalled in this connection that arterial vessels constitute the most important part of the resistance vessels, while the veins by far dominate the capacitance section. The above-mentioned differences in vascular structure must play an important functional role and may strongly contribute to the observed differences in configuration of the frequency-response curves of the resistance and the capacitance vessels.

Also the fact that the computed maximal percentage decrease in the internal radius of the resistance vessels appears to be bigger than that of the capacitance vessels can, partly or even wholly, be ascribed to the above-mentioned wall/lumen relationships between the two vascular sections. Fig. 12 makes it clear that a high wall/lumen ratio, like that existing in arterial vessels, tends to intensify the luminal reduction induced by the smooth muscle contraction while such a factor probably is of almost no importance in thin-walled vessels like veins. It is, of course, also possible that the smooth muscle cells of the resistance vessels in fact shorten more than those of the capacitance vessels on maximal neurogenic activation. To this comes the fact that presumably some of the smallest resistance vessels become plugged on constriction by blood cells, giving an effect that would simulate an especially intense luminal reduction. Thus several factors may in fact contribute towards the observed difference in extent of constriction between the resistance and the capacitance vessels.

Another factor that will tend to displace the frequency-response curve of the resistance vessels somewhat to the right, is the influence of so-called vasodilator metabolites released from the tissues. Any neurogenically induced flow restriction will somewhat raise the local metabolite concentration, which will tend to counteract the excitatory influence of the constrictor fibre transmitter. It seems as if the resistance vessels are relatively more sensitive to this counteracting influence: these vessels mostly exhibit a clear-cut reactive dilatation on interruption of constrictor fibre stimulation, which is generally not the case with the capacitance vessels, as already mentioned in chapter III. Also, other experiments in this laboratory, which have dealt in more detail with the reactions of the resistance and capacitance vessels in reactive hyperaemia, seem to support this view (KJELLMER, unpublished observations). It is easy to deduce from the frequency-response curve of the resistance vessels, shown in Fig. 8, that the accumulation of vasodilator metabolites, obtained at 8 impulses/sec should be almost as strong as that obtained at 16 impulses/sec, as the flow reduction is only slightly different in the two cases. The local noradrenaline concentration, on the other hand, can be expected to be roughly twice as big at 16 as at 8 impulses/sec, assuming that a given quantity of the constrictor fibre transmitter is released per shock and that the transmitter release mechanism is not exhausted (cf. ROSENBLUETH 1950, p. 88, BROWN and GILLESPIE 1957). The dilator influence of the accumulated vasodilator metabolites should thus be put in a somewhat better competitive position in relation to the constricting influence of the adrenergic transmitter at the lower discharge rates. This will tend to move the frequency-response curve of the resistance vessels towards the right, a mechanism that has previously been studied from a somewhat different point of view (FOLKOW 1952). On the other hand, the frequency-response curve for the capacitance vessels should not be much changed by such factors, since their smooth muscles did not seem to be much affected by metabolites.

As previously discussed (chapter III) the sympathetic effect on the capacitance vessels was essentially due to an *active* constriction of the smooth muscles, though a minor component of the recorded effect must be a consequence of a passive-elastic recoil of these vessels, caused by the lowering of the transmural pressure gradient. A similar passive-elastic recoil mechanism, superimposed on the active constriction, will presumably also, but to a still smaller degree, occur in the resistance vessels, as these vessels are also to some extent distensible (*e. g.* FOLKOW and LÖFVING 1956). Curves representing solely the active vasoconstriction in relation to constrictor fibre discharge rate in these two sections can, of course, not be *exactly* deduced from the records of blood flow and tissue volume. It seems, however, plausible that both curves, especi-

ally that representing the capacitance vessels, would, if anything, be displaced to the left, could the passive-elastic component be excluded. The elastic recoil can namely be expected to be relatively more pronounced at the highest stimulation frequencies because of the more pronounced fall in intravascular pressure then occurring within and beyond the resistance vessels.

In this connection it might be of interest to discuss also whether there is any evidence of a difference in *rate* of constriction and relaxation of the smooth muscles of the resistance and the capacitance vessels. Already the tracings illustrated in Fig. 3 indicate that no such more significant difference exists, and a further careful analysis of numerous stimulation effects at different rates in about 40 experiments supports this view. In all cases a fully developed response of both the resistance and the capacitance vessels was reached within 20—60 sec, generally 30—40 sec, and in each separate case there was, an almost exact accordance in the rate of the vasoconstriction within the two sections. Also the rate of relaxation of the smooth muscles, after stimulation ended, was essentially the same in the two vascular sections in a given case, which is illustrated for example in Fig. 7. The rate of smooth muscle relaxation was, however, often more variable than the constriction time, though the events in the two vascular sections were always co-ordinated in a given situation. Thus, the relaxation was generally quite rapid on cessation of stimulation and if the frequency applied was below 6—8 impulses/sec, it never surpassed 30—60 sec. However, the relaxation was much retarded both in commencement and in rate, at higher, 'supraphysiological' frequencies. The time interval between the interruption of the stimulation and the beginning of the relaxation was found to comprise less than 5 sec at the lower stimulation frequencies. At rates of stimulation exceeding about 6/sec, this 'latency period' was, however, prolonged, amounting to 5 — 15 sec, and a complete relaxation to the initial state at the higher frequencies was often not obtained until after some minutes. This finding has previously been shown in resistance vessels (Folkow 1952 a, Celander 1954), and has thus now been demonstrated also in capacitance vessels. The phenomenon of delayed relaxation at high rates of stimulation is interpreted as being due to an excess accumulation of the adrenergic transmitter at the site of release, causing a prolonged elimination time of the substance with a certain overflow as a consequence (for details see Celander 1954). This is also in agreement with more recent studies on the elimination of the adrenergic transmitter (Brown and Gillespie 1957).

2. Secondary effects on transcapillary filtration exchange

a. Results. Besides the effects on the resistance and capacitance vessels, Fig. 7 also illustrates the effects on transcapillary filtration secondary to sympathetic stimulation. The second, slow and fairly continuous phase of volume reduction on sympathetic stimulation has been attributed to a decreased capillary pressure, causing an influx of extravascular fluid into the circulatory system (for details see chapter III). Under the prevailing experimental conditions this must be due to a relatively stronger increase of precapillary than postcapillary resistance. The absorbed extravascular fluid will thus be mixed with and drained together with the perfusing blood. As long as the absorption is not so extensive as to affect more significantly counteracting factors, governing outward filtration across the capillary walls according to the Starling hypothesis, the volume curve should continuously decline at a steady rate, provided no reactive changes in smooth muscle tone and hence capillary blood pressure occur. Fig. 7 illustrates how the rate of this absorption process across the capillary walls was influenced by sympathetic stimulation at various frequencies. The slope of the second, slow phase of volume reduction, representing transcapillary influx, is here indicated by the adjacent dotted lines. It is evident that the slopes become steeper with increasing frequency of stimulation, revealing a successively more rapid fluid absorption or, in other words, a more and more reduced capillary pressure. From these slopes the transcapillary inflow, expressed in ml/min, could be estimated in each experiment and was generally found to be maximal at about 16 impulses/sec, *i. e.* at that rate of stimulation which produced the most intense constriction of the resistance vessels.

Fig. 13 illustrates by a diagram, deduced from a representative experiment, how vasoconstrictor fibre stimulation at various frequencies affected the capacitance and resistance vessels as well as the transcapillary inflow, all effects being calculated in percentage of maximum responses obtainable. The curve representing transcapillary inflow roughly follows the curve deduced for the resistance vessels. At 8 impulses/sec and above, the values coincide completely, while at lower rates of stimulation there is a small though distinct difference between them, forming a deviation in the absorption curve. The increase of transcapillary inflow is here relatively smaller than the increase of resistance at stimulation frequencies around 2—4 impulses/sec, thus at the very frequencies where the slope of constriction increase of the capacitance vessels is relatively steeper than that of the resistance vessels. This peculiar deviation in the curve was so regularly seen that it cannot be taken as an accidental event and it will be further discussed below.

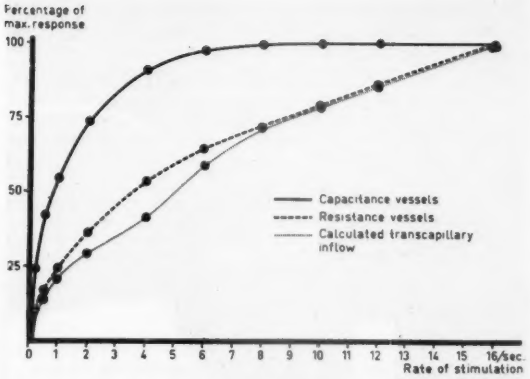

Fig. 13. Correlation between effects of vasoconstrictor fibre stimulation at various rates on capacitance vessels (continuous line), resistance vessels (dashed line) and on transcapillary inflow of extravascular fluid (dotted line), all effects expressed in percentage of the respective maximum ones obtainable. The curve representing transcapillary inflow follows roughly that deduced for resistance vessels, although a slight deviation exists in lower frequency range. For discussion see text.

It was shown in chapter III how — analogous to the filtration coefficient — the 'absorption coefficient' (amount of fluid absorbed/min/mmHg pressure change/100 g tissue) could be estimated when the vessels were not exposed to sympathetic influence (Fig. 2 *B*). This 'absorption coefficient' at 'basal vascular tone' was determined in each experiment, as was the rate of the transcapillary inflow during the periods of sympathetic stimulation (see Fig. 7). It was then possible to calculate roughly how much mean capillary pressure must have been decreased by a given frequency of sympathetic stimulation. In Fig. 7 the calculated decrease of capillary pressure at various frequencies of sympathetic stimulation is indicated in approximate figures. The mean capillary pressure fall at the most effective sympathetic stimulation (16 impulses/sec) comprised here up to about 15 mm Hg. In some experiments the maximal capillary pressure fall did not seem to exceed 10—12 mm Hg.

The transcapillary influx of extravascular fluid into the circulatory system during constriction is, as mentioned above, a fairly slow process characterized especially by its steadiness as long as the transcapillary pressure gradient and the size of the available capillary surface are constant. The rate of transcapillary inflow was also found to be relatively constant during the sympathetic stimulation period, if this was not too prolonged. If, however, the duration of the stimulation was extended beyond say 2 to 3 minutes, the steady decline in the volume curve tended to decrease gradually and finally

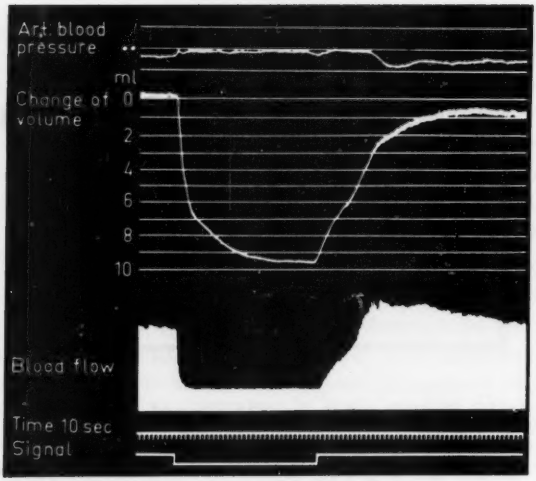

Fig. 14. Cat 3.0 kg. Chloralose-uretane. Effects of lumbar vasoconstrictor fibre stimulation at 6 impulses/sec. Note that transcapillary inflow, judged from the latter part of the declining volume curve, was first continuous but later on retarded and finally stopped where the volume curve levels off, despite the fact blood flow remained stable. For discussion see text.

it levelled off horizontally. This occurred in spite of the fact that blood flow remained at its lowered level and thus the sympathetic effect on the resistance vessels proved to be unchanged (see Fig. 14), a fact that will be discussed below.

The sympathetic stimulation thus induced not only an 'intravascular fluid mobilization', inherent in the constriction of the capacitance vessels, but also an 'extravascular fluid mobilization' into the circulatory system, secondary to the relatively and absolutely stronger constriction of the precapillary resistance section. It is important to know the quantitative interrelationship between these two forms of fluid mobilization, which will both affect cardiovascular dynamics, and this relationship is illustrated in Fig. 15. The 'intravascular blood mobilization' is indicated by continuous lines and the 'extravascular fluid mobilization' by dashed lines. The amounts of extravascular fluid passing into the vascular bed are judged, as mentioned above, by the second, slower slope of volume decrease obtained on sympathetic stimulation. The diagram shows the extravascular fluid volume passing into the vascular bed during the first two minutes, when it still is fairly rapid and not yet more significantly counteracted by secondary changes of diffe-

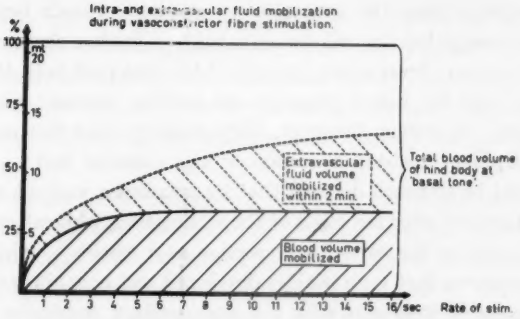

Fig. 15. Diagram illustrating the interrelationships between the 'intravascular fluid mobilization' — due to constriction of capacitance vessels — and the 'extravascular fluid mobilization' into the circulatory system occurring within 2 min — due to capillary pressure drop — at various rates of stimulation of the vasoconstrictor fibres of the hind parts of the cat (total bodyweight 3 kg). Arterial inflow pressure and venous outflow pressure kept constant. Note that the absorption of extravascular fluid became considerable first at such rates of stimulation where the intravascular blood mobilization was largely completed.

rent types. It can be seen from the figure that this transcapillary inflow is small but by no means insignificant at such relatively moderate increases of discharge rate as can be expected to be well within the 'physiological' range. However, the 'extravascular fluid mobilization' becomes *considerable* first at such high rates of sympathetic discharge where already the 'intravascular fluid mobilization' is largely completed. It is questionable whether such higher rates of sympathetic discharge, 6 to 10 impulses/sec or higher, ever occur under *in vivo* conditons, except for short episodes under situations of extreme stress. The implications of the 'extravascular fluid mobilization' for cardiovascular dymanics will be further commented on below (see chapter VI).

b. Comments. As has already been stated in chapter III, there is no doubt that the vasoconstrictor fibre stimulation induces a transcapillary inflow of extravascular fluid, at least during the first period of sympathetic activation. Among other things, it was shown that the passing blood actually became diluted, (plasma protein content decreased), during this slow phase of volume decrease, proving that tissue fluid must have entered the blood stream. However, the gradual cessation of this inward flow of extravascular fluid across the capillary walls, in spite of continuing sympathetic stimulation with seemingly sustained smooth muscle contraction, calls for some comments. It can, for instance, be argued that the cessation of transcapillary influx might be due to a protracted gradual increase in postcapillary resistance,

while at the same time the precapillary resistance vessels begin to relax, *e. g.* due to accumulated vasodilator metabolites. Such a change would raise the capillary pressure level again, in spite of the fact that both the *total* resistance to flow, and the inflow pressure and outflow pressure remain essentially unchanged. It seems, however, very unlikely that the nervous effect on the postcapillary resistance section of the vascular bed — the smaller veins — should be so much delayed that its maximum was not reached until more than 2 minutes after the onset of the stimulation, while all other vascular sections — including the capacitance section as a whole — exhibited almost immediate responses that were rapidly developed and equal in rate. However, it is not impossible that gradually the postcapillary resistance does in fact increase to a certain extent, for reasons that are quite unrelated to smooth muscle contraction. It is known that slowing of the flow rate, probably occurring at least on the venous side in connection with vasoconstriction, can cause aggregation of blood cells, which appears to be especially prominent within the small veins (*e. g.* GELIN 1956). This, other things being equal, might to some extent increase postcapillary resistance simply owing to the locally raised viscosity of the blood, in turn again raising mean capillary pressure. — Another reasonable explanation of the levelling off of the slow phase of the volume decrease seems to be the following: there is some evidence that a smaller or larger section of the precapillary sphincters will actually close on sympathetic stimulation due to a direct influence of constrictor fibres and/or to the decrease of regional intravascular pressure (FOLKOW and MELLANDER 1960). This will result in an obstruction of the arterial inflow into the corresponding capillaries. Even if these capillaries do not collapse but still contain stagnant blood at a low hydrostatic pressure, the extravascular fluid that passes into them is now no longer taken up by a passing blood stream. Even though some drainage of these proximally closed capillaries may occur *via* their venous ends out into the venous blood stream, the inward passage of tissue fluid will soon lower their intracapillary colloid osmotic pressure enough to decrease the 'inward filtration gradient' towards zero. In such proximally closed capillaries the inward passage of tissue fluid will therefore very soon come to a standstill, while it will proceed fairly undisturbed in those capillaries where blood flow is maintained. Net transcapillary filtration exchange will then be stabilized at a new, decreased level. Further, sooner or later the inward filtration across any capillary must come to a standstill, when the part of the surrounding extracellular fluid which can be mobilized is drained enough to increase tissue colloid osmotic pressure and lower tissue hydrostatic pressure, to create again a transcapillary equilibrium. — The above-mentioned mechanisms might all be involved and are

able to explain why the absorption process at sympathetic stimulation was gradually retarded and finally stopped. In no case was there evidence of an *outward* filtration of fluid from the capillaries during sympathetic stimulation, which would have been the case if the vasoconstrictor fibre influence were relatively more intense on the postcapillary than on the precapillary resistance section.

In recent studies of the cutaneous vessels of the dog's paw (KELLY and VISSCHER 1956, LEE and VISSCHER 1957) it was, however, observed that the pressure in the small veins, measured by a direct micro-cannulation technique or by an indirect micro-chamber method, often rose considerably during sympathetic stimulation and even more after cessation of stimulation, when the pressure in small arteries began to fall. These data may suggest that the postcapillary resistance vessels should in fact be relatively more strongly constricted than the precapillary ones at sympathetic vasoconstrictor fibre activation. It was also postulated by these investigators that such a neurogenic influence might be of importance in oedema formation. However, if this were a general feature during sympathetic discharge it would be expected that, in the present study also, mean capillary pressure should have risen at sympathetic stimulation. This, in turn, would have resulted in a fluid filtration out into the tissue spaces with an *increase* of the recorded tissue volume as a consequence. Such a type of reaction was not observed in a single case in the present experiments, which comprised altogether more than 400 stimulations of the vasoconstrictor fibres. No doubt, however, the postcapillary resistance can also increase rather markedly during sympathetic stimulation, but throughout the present experiments this increase always appeared to be smaller than that of the precapillary resistance, both in absolute and relative figures. The situation can, of course, be different if, for one reason or another, the constrictor fibres of the postcapillary resistance vessels are more strongly activated than those of the precapillary ones. There is also a possibility that the mechanical manipulation of the veins — to a greater or lesser extent unavoidable when the micro-cannulation technique of KELLY and VISSCHER, is employed — may in itself have caused a venoconstriction contributing to the neurogenically induced one, and hence have led to a rise in local venous pressure. It should further be noted that these investigators, surprisingly enough, often observed tetanic contractions of the skeletal muscles of the limb during sympathetic stimulation. It may be possible that at least some of their recorded pressure increases in the small veins were secondary to such muscle contractions, squeezing out muscle blood into the neurogenically constricted cutaneous veins. It is somewhat puzzling that tubo-curarine abolished both this tetanic muscle contraction

and the rise of small venous pressure, while succinyl choline was said to abolish only the skeletal muscle contractions. Further, the stimulation frequencies used in the experiments of Lee and Visscher were generally far beyond the 'physiological range' (10—38/sec), under which circumstances adrenergic transmitter overflow is known to occur (*e. g.* Celander and Mellander 1955). Such an overflow will markedly prolong the contractions and may also in other respects affect the vascular reactions. — Recent studies by Davis and Hamilton (1959) are in good agreement with the results of the present investigation, as they indicate that the reactions of small arterial and venous cutaneous vessels are such that an outward filtration during sympathetic stimulation can hardly take place. Therefore, if oedema formation occurs in the intact organism only as result of vasoconstrictor fibre activation with no major changes in arterial and central venous pressures it may, in fact, suggest a differentiated sympathetic activity with a relatively higher discharge rate in the constrictor fibres supplying the postcapillary resistance vessels.

The peculiar deviation in the curve for capillary absorption as correlated to the curve for resistance vessel response during sympathetic stimulation (Fig. 13) calls for some remarks. As has been mentioned, this was a regular finding and must therefore have some reasonable haemodynamical explanation. It should here be remembered that the postcapillary resistance vessels are essentially identical with the thin-walled small veins. It is therefore quite probable that the frequency-response curve of this very vascular section will be closely similar to that of the capacitance vessels as a whole, as these vessels are mainly made up of the venous bed as such. It then follows that the precapillary resistance vessels, (small arteries with higher wall/lumen ratios), and the postcapillary ones, (small veins), should have frequency-response curves of different shapes, in principle corresponding to those of the resistance vessels as a whole and the capacitance vessels as a whole, respectively (Fig. 8). This circumstance will influence the rate of inward filtration at different discharge rates of the sympathetic nervous system in a way that reflects the characteristic differences in constrictor response within the two resistance sections. Thus, the constriction change of the postcapillary resistance section can be expected to be especially marked at discharge rates up to 4—6 impulses/sec, and this will have the consequence that the *ratio* between the pre- and postcapillary resistances will here be less markedly increased than at higher discharge rates. In the higher discharge range, on the other hand, precapillary resistance does still increase, while the postcapillary resistance can then be expected to be already nearly maximal. Other things being equal, this implies that the mean hydrostatic capillary

pressure is proportionally *less* decreased at low discharge rates than at those above 4 to 6 impulses/sec. Hence, at lower discharge rates the inward transcapillary flow of extravascular fluid will be relatively smaller than would have been expected only from the increase of the total regional resistance. At higher rates, on the other hand, it can be expected to increase more in direct proportion to the increase in total regional resistance, as then the resistance increase is essentially caused by the precapillary resistance vessels.

CHAPTER V

Effects of adrenal medullary hormones on resistance and capacitance blood vessels

The purpose of this part of the study was to investigate the effects of the adrenal medullary hormones, released by graded splanchnic nerve stimulation, on the resistance and the capacitance vessels in the hind parts of the cat, and to compare these responses quantitatively with those induced by graded excitation of the vasoconstrictor fibres. Further, the effects of l-adrenaline and l-noradrenaline on the two consecutive vascular sections were studied when these two catechol amines were infused separately, in amounts approximately corresponding to the range of hormone release from the adrenal medullae.

Since the discharge rate of the sympathetic nervous system hardly ever appears to exceed about 10 impulses/sec in the intact organism (for lit. see FOLKOW 1955, 1956 a), stimulation frequencies above this rate were only used exceptionally in this series of experiments. There is evidence that, at this maximal rate, a total of roughly 5 μg/kg/min of catechol amines are released from the two adrenal medullary glands of the cat (CELANDER 1954). This amount was therefore set as the highest dosage limit for intravenous infusions of l-adrenaline and l-noradrenaline. — For technical details see chapter II.

1. Effects on resistance vessels as compared with effects on capacitance vessels

Fig. 16, 17 and 18, based on one and the same experiment, illustrate the typical vascular responses to graded stimulations of the vasoconstrictor fibres and of the sympathetic secretory nerves of the left adrenal medulla. In addition, the effects of intravenous infusions of l-adrenaline and l-noradrenaline are illustrated. A time interval of 5 minutes was allowed for recovery between each experimental step.

Fig. 16 demonstrates first (at *A*), the effects of a close arterial injection of a supramaximal dose of acetylcholine (20 μg), given to check the extent of 'basal vascular tone' present after cutting the vasomotor fibres. This basal

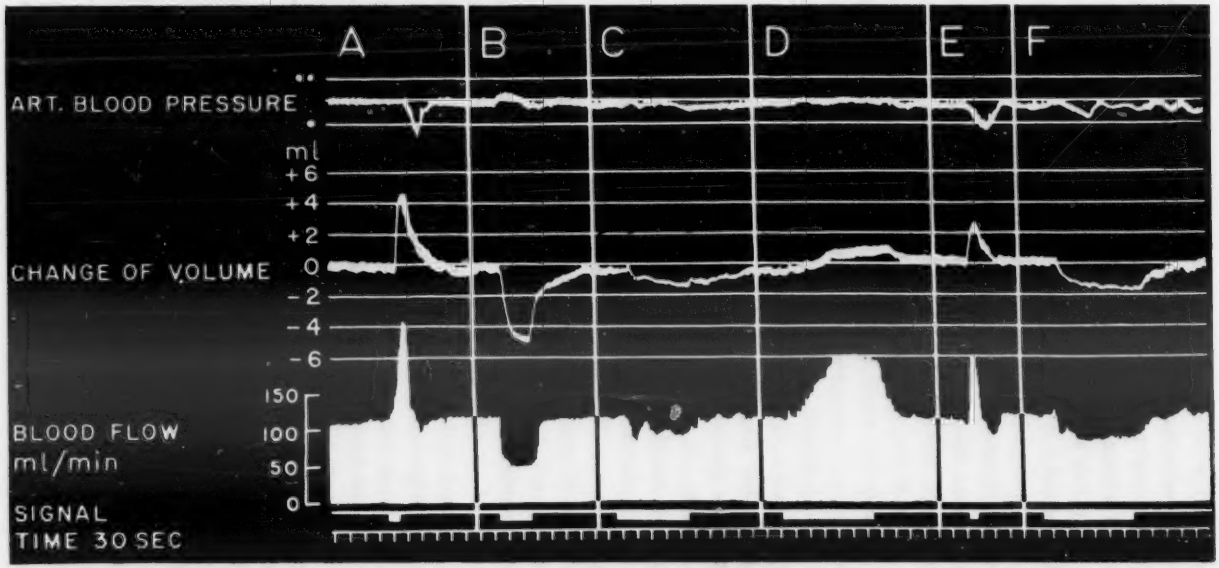

Fig. 16. Cat 3.4 kg. Uretane. Adrenergic neuro-hormonal influence on resistance and capacitance vessels in skin-muscle region (*B*, *C*, *D*, *F*).

A. Close arterial injection acetylcholine (20 μg).
B. Stim. lower abdominal symp. chains (1 impulse/sec).
C. Stim. left splanchnic nerves (2 impulses/sec).
D. I. v. infusion l-adrenaline (0.4 μg/kg/min).
E. Close arterial injection acetylcholine (1 μg).
F. I. v. infusion l-noradrenaline (0.4 μg/kg/min).

For further details see text.

tone is normally rather pronounced in tissues like the skeletal muscles, at least as regards their resistance vessels (see LÖFVING and MELLANDER 1956), and it was therefore considered important to know its extent in the present preparation, as also l-adrenaline, known to dilate the vessels of the muscles, was to be tested. By this acetylcholine injection it was demonstrated that the vascular bed possessed a good 'basal tone', as the regional flow resistance decreased to 1/2—1/3 of the initial value and the capacitance vessels increased their blood content by about 5 ml. — Fig. 16 *B* and *C* illustrate the quantitative relationship between the vascular reactions induced by the 'direct nervous' and the 'hormonal' link of the sympathetic adrenergic system at low discharge rate. In 16 *B* the vasoconstrictor fibres of the hind parts were stimulated at 1 impulse/sec, while the secretory nerves of the left adrenal medulla were excited at 2 impulses/sec in 16 *C* in order to simulate the condition created if both adrenal medullae had been activated with 1 impulse/sec (see p. 00). Stimulation of only the left adrenal was justified, as control experiments showed that the effects of unilateral splanchnic stimulation conformed well to those obtained when the nerves of *both* adrenal glands were excited at half the rate. It is evident that the vasoconstrictor fibre effects were much more pronounced than those caused by the hormonal link, with regard to both the resistance and the capacitance sections of this vascular bed. Regional resistance to flow increased about 120 per cent and 30 per cent respectively. The volume decrease due to capacitance vessel constriction comprised about 4 ml and 1 ml respectively. — In Fig. 16 *D*, l-adrenaline was infused intravenously in a dose that should approximately correspond to the total amount of catechol amines released from the adrenal medulla (Fig. 16 *C*). In the hind parts, mainly consisting of skeletal muscle tissue, this small dose of l-adrenaline (0.4 μg/kg/min) induced a marked dilator response of the resistance vessels, as could be expected, regional flow resistance decreasing to about half the initial value. It should be noted, however, that there was only a very slight simultaneous increase in the volume of the hind parts, which indicated that the dilatation of the capacitance vessels was almost insignificant. The volume curve shows here first an initial, brief incline of less than 1 ml, completed at the same moment as the resistance vessels had fully developed their dilator response. After this rapid phase of increase in volume, there was a distinct bend in the volume curve, and a continuous but slower increase of tissue volume followed, which persisted during the remaining period of steadily maintained dilatation of the resistance vessels. In analogy with previously described experimental analyses, the initial rapid increase in volume is interpreted as being due to a slight dilatation of the capacitance vessels. The subsequent continuous and slower increase

should then be due to a filtration of fluid from the circulatory system out into the tissues, secondary to an increased capillary pressure. Under the prevailing circumstances an increased capillary pressure should be created only if the precapillary resistance vessels were relatively more dilated than the postcapillary ones, an interpretation which will be further discussed below. – In Fig. 16 *E*, acetylcholine was injected intra-arterially in such an amount as to induce the same degree of dilatation in the resistance vessels as that caused by adrenaline in 16 *D*. Note that acetylcholine then induced about three times as great an effect on the capacitance vessels as did l-adrenaline. The quantitative relation between these vascular effects was essentially the same if acetylcholine was steadily infused instead of injected. — In Fig. 16 *F*, finally, l-noradrenaline was infused intravenously in a dose equivalent to that of l-adrenaline and to the catechol amount supposed to be released at stimulation of the left splanchnic nerves (Fig. 16 *D* and *C* respectively). Noradrenaline brought about a pure constriction of both the resistance and the capacitance vessels, judging by a 25 per cent increase in peripheral resistance and a 2 ml decrease in volume respectively. Note that the volume curve shows first a rather rapid decline and then a slower one — as was the case during vasoconstrictor fibre stimulation. These two phases presumably also here indicate an initial active constriction of the capacitance vessels and a steady absorption of extravascular fluid respectively. The principles of interpretation of the recorded changes in volume with regard to the quantitative distinction between the hormonal constrictor effects of the capacitance vessels and the capillary filtration effects, are outlined in section 2 of this chapter.

Fig. 17 demonstrates the typical vascular responses obtained at a somewhat higher level of sympathetic discharge. In Fig. 17 *A* the sympathetic nerves of the hind parts were stimulated at 2 impulses/sec and at *B* the left splanchnic nerves were activated at 4 impulses/sec. At *C*, l-adrenaline and at *D*, l-noradrenaline were infused intravenously in doses of 1 μg/kg/min. The vasoconstrictor responses of both the resistance and the capacitance vessels to sympathetic and splanchnic stimulation and to l-noradrenaline infusion were here more pronounced than those shown in Fig. 16. In both vascular sections the response to adrenaline was now converted into a vasoconstriction instead of a vasodilatation. Regional resistance to flow increased about 160 per cent at *A*, 40 per cent at *B*, 20 per cent at *C* and 60 per cent at *D*. The volume decrease due to capacitance vessel constriction comprised about 5 ml at *A*, 1.8 ml at *B*, 1.2 ml at *C*, and 2.9 ml at *D*.

Fig. 18, lastly, demonstrates the vascular responses obtained at about the maximal 'physiological' rate of sympathetic discharge, here showing still

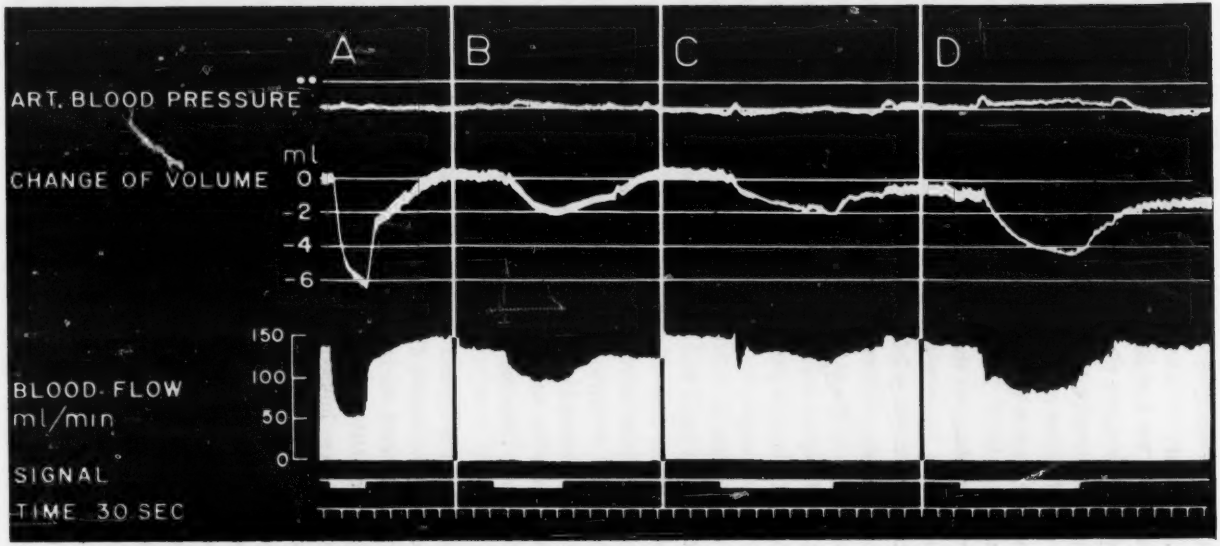

Fig. 17. Cat 3.4 kg. Uretane. Adrenergic neuro-hormonal influence on resistance and capacitance vessels in skin-muscle region.

A. Stim. lower abdominal symp. chains (2 impulses/sec).
B. Stim. left splanchnic nerves (4 impulses/sec).
C. I. v. infusion l-adrenaline (1 μg/kg/min).
D. I. v. infusion l-noradrenaline (1 μg/kg/min).

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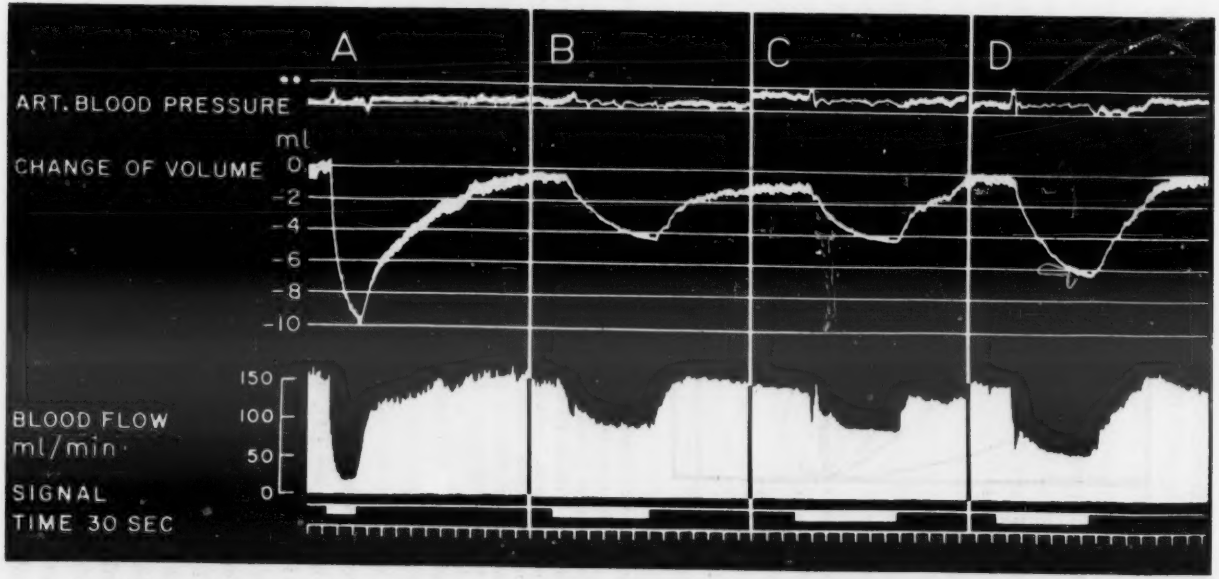

Fig. 18. Cat 3.4 kg. Uretane. Adrenergic neuro-hormonal influence on resistance and capacitance vessels in skin-muscle region.

A. Stim. lower abdominal symp. chains (10 impulses/sec).
B. Stim. left splanchnic nerves (20 impulses/sec).
C. I. v. infusion l-adrenaline (5 μg/kg/min).
D. I. v. infusion l-noradrenaline (5 μg/kg/min).

For details see text.

Fig. 19 is to be exchanged for Fig. 21.

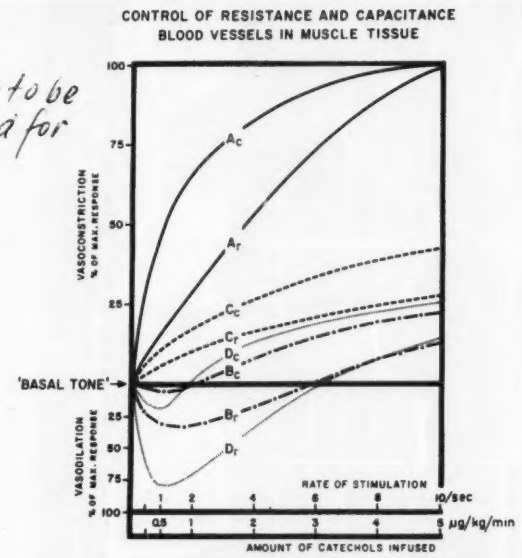

Fig. 19. Adrenergic neuro-hormonal control of resistance and capacitance vessels in skin-muscle region, (mean 5 experiments):

Symp. vasconstrictor fibres: A_r resistance vessels; A_c capacitance vessels. *Both* adrenal medullae: B_r resistance vessels; B_c capacitance vessels. 1-noradrenaline: C_r resistance vessels; C_c capacitance vessels. 1-adrenaline: D_r resistance vessels; D_c capacitance vessels. Curves A and B upper abscissa, curves C and D lower abscissa. *Left ordinate:* percentage values; maximal constrictor effects = effects of vasoconstrictor fibre stim. at 10 impulses/sec; maximal vasodilator effects = effects of close arterial injection of acetylcholine, 20 µg. *Right ordinates:* 1. PRU = relative peripheral resistance units. 2. Induced changes of regional blood volume, ml/100 g tissue. For further details see text.

stronger vasoconstrictor effects. The lumbar sympathetic chains were stimulated at 10 impulses/sec (*A*), and the secretory nerves of the left adrenal medulla at 20 impulses/sec (*B*) — approximately corresponding to the effect that should be induced by an activation at a rate of 10 impulses/sec of both glands. 1-adrenaline and 1-noradrenaline were here infused in doses of 5 µg/kg/min (*C* and *D* respectively). Regional resistance to flow increased about 650 per cent at *A*, 70 per cent at *B*, 60 per cent at *C* and 140 per cent at *D*. The volume decrease due to capacitance vessel constriction comprised about 7 ml at *A*, 3 ml at *B*, 2.8 ml at *C* and 4 ml at *D*.

To allow a closer comparison of the graded responses of the resistance and the capacitance vessels in the combined skin-muscle region to vasoconstrictor nerve stimulation and to blood-borne catechol amines, the diagram shown in Fig.

19 was deduced. The frequency-response curves for the two vascular sections are here illustrated. These curves show the mean effects of vasoconstrictor fibre stimulation and activation of the *two* adrenal medullae in five technically entirely successful experiments. Further the dose-response curves, deduced from the vascular effects of catechol amine infusions in 'physiological' concentrations, are also indicated. The steady state figures of blood flow and blood volume, when the hind parts were in 'resting' equilibrium and the blood vessels exhibited their 'basel tone', constitute the 'baseline' of the diagram. All vascoconstrictor responses are expressed as a percentage of those obtained on constrictor fibre stimulation at 10 impulses/sec, simply because this rate can be considered as the approximate highest discharge limit under *in vivo* conditions. Similarly, all vasodilator responses are expressed as a percentage of the maximum obtainable dilator responses of both vascular sections, *i. e.* the dilator responses induced by intra-arterial injections of acetylcholine in supramaximal concentrations. Along the right hand ordinates in the diagram in Fig. 19 the vascular effects are indicated also in terms of relative peripheral resistance units for the resistance vessels and amounts of blood translocated per 100 g of tissue for the capacitance vessels. Of course these values vary to some extent in different animals and those here indicated should be regarded as approximate mean values.

The curves in Fig. 19 clearly demonstrate the dominating role of the vasoconstrictor fibres in the centrally directed constrictor control of both the resistance (A_r) and the capacitance sections (A_c), as compared to the influence of the adrenal medullary hormones (curves B_r and B_c = splanchnic stimulation; curves C_r and C_c = l-noradrenaline infusion; curves D_r and D_c = l-adrenaline infusion). It is further clear from this diagram that adrenaline in low concentrations, also in a combined skin-muscle preparation, exerts an overall powerful vasodilator influence on the resistance vessels (D_r), while it hardly dilates the capacitance vessels at all (D_c).

It is well known from several other studies that the vasodilatation induced by adrenaline on the resistance vessels is confined to muscle regions, while cutaneous vessels respond to all adrenaline concentrations with constriction. Therefore, to analyse in more detail the dilator effects of adrenaline, a series of experiments was performed also on a 'pure' skeletal muscle preparation. Fig. 20 illustrates such an experiment where a 'pure' muscle preparation was used. In *A* of Fig. 20, an l-adrenaline infusion of 0.3 μg/kg/min induced a considerable dilatation of the resistance vessels and, for comparison, the same degree of dilatation of these vessels was brought about by infusing a low concentration of acetylcholine (*B*). The dilator response of the capacitance vessels to adrenaline was here again very weak, only about a fifth

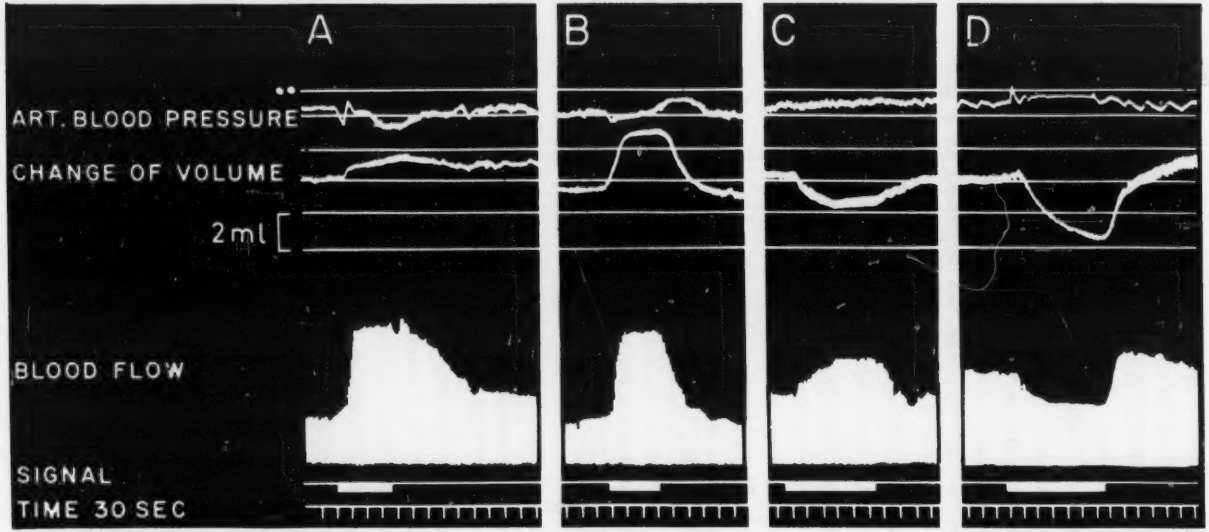

Fig. 20. Cat 3.5 kg. Uretane. Muscle region. *A*. I. v. infusion of adrenaline (0.3 μg/kg/min). *B*. I. a. infusion of acetylcholine in such a dose. (1.7 μg/kg/min) as to induce the same degree of dilatation of the resistance vessels as in *A*. The dilatation of the capacitance vessels (rapid initial incline of volume curve) is then 4—5 times bigger for acetylcholine than for adrenaline. The slow volume increase during steadily maintained dilatation, due to fluid filtration, is, however, more rapid in *A* than in *B*. *C*. I. v. infusion of adrenaline (0.7 μg/kg/min). Resistance vessels dilated while capacitance vessels constricted. During the period of maintained resistance vessel dilatation an outward filtration occurred as indicated by the slowly inclining volume curve. *D*. I. v. infusion adrenaline (3 μg/kg/min). Both resistance and capacitance vessels constricted.

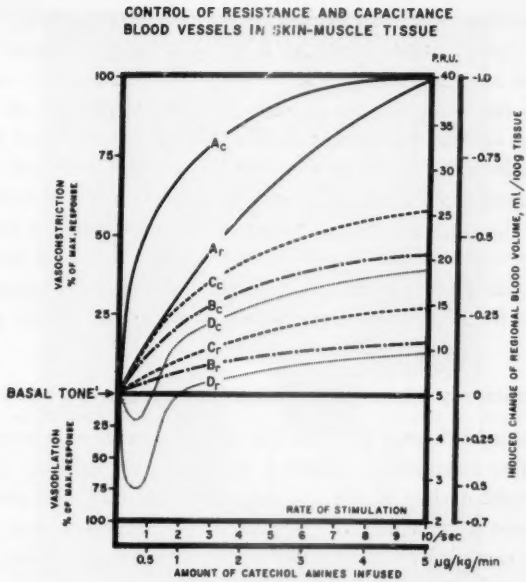

Fig. 21 is to be exchanged for Fig. 19

Fig. 21. Adrenergic neuro-hormonal control of resistance and capacitance vessels in muscle region, (mean 5 experiments):

Symp. vasoconstr. fibres: A_r resistance vessels; A_c capacitance vessels. *Both* adrenal medullae: B_r resistance vessels; B_c capacitance vessels. l-noradrenaline: C_r resistance vessels; C_c capacitance vessels. l-adrenaline: D_r resistance vessels; D_c capacitance vessels. Curves A and B upper abscissa, curves C and D lower abscissa. *Ordinate:* percentage values; maximal constrictor effects = effects of vasoconstrictor fibre stim. at 10 impulses/sec; maximal vasodilator effects = effects at close arterial injection of acetylcholine, 20 µg. For further details see text.

of that induced by acetylcholine when given in a dose that induced an equal dilatation of the resistance vessels. — In Fig. 20 *C* the infused dose of l-adrenaline was increased to 0.7 µg/kg/min, giving a less pronounced, but still appreciable dilatation of the resistance vessels. Now, however, the capacitance vessels responded with a definite constriction. Within one and the same vascular bed it was thus possible to elicit *opposite* responses of the resistance and the capacitance sections to a given dose of adrenaline. — The slow and more continuous phase of increase in volume after the initial change in volume in Fig. 20 *A*, *B* and *C* is probably due to an outward transcapillary filtration and will be discussed below. — In Fig. 20 *D*, finally, where the dose of l-adrenaline was further increased (3 µg/kg/min), both the resistance and the capacitance vessels responded with a constriction.

The neuro-hormonal effects evoked in the resistance and the capacitance vessels in the 'pure' muscle region at different discharge rates of the sympathetic nervous system, are summarized in terms of frequency-response and dose-response curves in Fig. 21, in analogy with the diagram in Fig. 19. If this diagram is compared with that of Fig. 19, it can be seen that the vascular responses to adrenaline conformed in principle to those obtained in the combined skin-muscle region, although certain quantitative differences are evident. This was also the case with regard to the response to stimulation of the adrenal medullary nerves and with regard to the administration of noradrenaline. The greatest difference concerns the vasodilator effect of adrenaline, which, as could be expected, was more prominent in the 'pure' muscle preparation.

2. Secondary effects on transcapillary filtration exchange

It was shown in chapter III that the change in volume recorded at vasoconstrictor fibre stimulation exhibited two distinctly different phases. The initial and rapid decline of the volume curve was due to a constriction of the capacitance vessels and the second, slow and continuous decrease in volume was caused by an absorption of extravascular fluid, presumably secondary to a lowered capillary pressure. Both these phases were clearly shown also in the present series of experiments (see Fig. 16 *B*, 17 *A* and 18 *A*). It was also previously shown that a fully developed constrictor response was reached simultaneously within the resistance and the capacitance vessels, *i. e.* the 'constriction time' of their smooth muscles was roughly identical. On this basis it appeared possible to determine to what extent the recorded decrease in volume was due to a constriction in the capacitance vessels and to what extent to absorption of extravascular fluid, even in such stimulation experiments where the initial fluid absorption was so great that a distinct 'bend' of the volume curve was not always seen. This principle proved to be useful also for analysing the volume shifts recorded when the vascular bed was exposed to the less rapid action of blood-borne catechol amines. The concentration of the intravenously administered substances is here only successively built up to a steady level in the studied vascular region, making the smooth muscle contractions more gradual than those induced by constrictor fibre stimulation. If also a transcapillary inflow of extravascular fluid takes place here, it can under such circumstances be expected to be more difficult to distinguish from the effect of constriction of the capacitance vessels, since a more distinct 'bend' of the volume curve may not be obtained. However, by extrapolating to the volume curve the point of the fully developed constriction of the resistance vessels, it seems possible to decide ap-

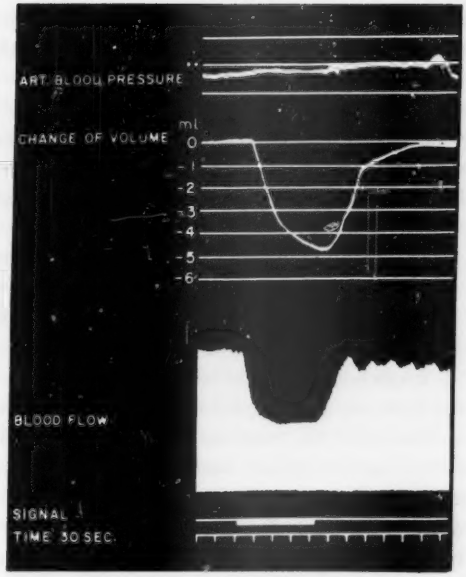

Fig. 22. Cat 3.4 kg. Uretane. Effects of intra-arterially infused l-adrenaline (5 μg/kg/min) on resistance and capacitance vessels in a skin-muscle region. A distinct bend in the volume curve can be seen, which permitted direct differentiation between the initial rapid phase of volume decrease, due to capacitance vessel constriction, and the subsequent slower phase of volume decrease, due to transcapillary inflow of extravascular fluid.

proximately to what extent the volume change is due to a constriction of the capacitance vessels and to a changed transcapillary fluid exchange (see Fig. 16, 17 and 18). Further, when the catechol amines were infused intra-arterially, reaching a steady concentration in the hind parts more quickly, an often distinct differentiation between the two phases of the volume curve appeared, similar to that recorded during vasoconstrictor fibre stimulation (Fig. 22). These results suggest that also when catechol amines were delivered by way of the blood stream the vasoconstrictor response was combined with an inflow of extravascular fluid into the intravascular compartment. In order to substantiate this interpretation further, the protein content of the plasma drained from the studied vascular region was determined at close intervals during catechol-induced vasoconstriction, as described on p. 00 (see also Fig. 6). It was then found that the plasma protein concentration of the venous outflow decreased significantly (sometimes up to 15 per cent)

during the catechol-induced vasoconstriction, and did so to an extent which was in accordance with what could be predicted from the above-mentioned extrapolated analysis of the volume curve. It therefore seems evident that blood-borne catechol amines, like the vasoconstrictor fibres, will affect the precapillary resistance vessels relatively more than the postcapillary ones. This means that their vasoconstrictor influence leads to a decrease in capillary hydrostatic pressure and hence to a flux of extravascular fluid into the intravascular compartment. The calculated fall in mean capillary pressure during l-noradrenaline infusion in maximal 'physiological' amounts, 5 μg/kg/min, comprised about 4 to 6 mm Hg. (For principles concerning this calculation see p. 00). This deduced capillary pressure fall was slightly less both during a similar 'maximal' adrenaline infusion, and during splanchnic stimulation at 'maximal' rates when a mixture of the two catechol amines should be released from the animal itself in similar concentrations. It should then be borne in mind that the vasoconstrictor effects of adrenaline on the resistance vessels in a muscle region were throughout less pronounced than those of noradrenaline. Note that arterial inflow pressure was usually kept constant in these experiments. However, if arterial inflow pressure in the hind parts was not controlled during intravenous infusions of catechol amines, there was generally still evidence of a certain transcapillary inflow during the catechol-induced constriction. This fact indicated that the regional increase of precapillary resistance was relatively more prominent than the increase in arterial inflow pressure.

It was technically more difficult to reveal whether adrenaline dilates the precapillary resistance vessels of the skeletal muscles relatively more than the postcapillary ones, causing an *outward* filtration. If this were so, relatively minute transcapillary shifts of fluid should occur, while blood flow is in fact much *increased*, leading to such small changes in the protein concentration of the venous outflow that they can hardly be measured with any accuracy. When, on the other hand, nerve stimulation or blood-borne catechol amines cause a *reduced* blood flow, a transcapillary shift can be more easily revealed, as then the changes of plasma protein concentration become more significant. Already the fact that adrenaline markedly increases blood flow, while regional blood volume only increases slightly (see Fig. 16 *D* and 20 *A*), suggests that the postcapillary resistance section may be relatively *less* dilated by adrenaline than the precapillary, arteriolar one. It should be realized that the postcapillary resistance vessels are essentially identical with the small veins, which also form an important part of the capacitance vessels (mainly the venous compartment of the vascular bed). The minute increase in regional blood volume proves that the veins in general are little,

if at all, dilated by adrenaline; and there are reasons to believe that the small veins behave in a similar fashion. Further, the fact that there occurred a slow and continuous increase in volume after blood flow had reached a constant level — *i. e.* when the smooth muscle relaxation of the resistance vessels was already fully developed and maintained constant — suggests that this slow volume increase is not due to a further relaxation of the capacitance vessels, but rather to a transcapillary outflow of fluid into the tissues. It can namely be expected that the 'dilatation time' should be of about equal duration in both resistance and capacitance vessels, in analogy to what was found to be the case with the 'constriction time' during vasoconstriction. Such an interpretation of the volume change during the adrenaline-induced dilatation was further supported by the following experimental steps, analogous to those performed previously (see chapter III, Fig. 5), but now in the opposite direction. By adjusting venous outflow pressure to a lower level during adrenaline infusion, thus decreasing capillary hydrostatic pressure during the continuous and slow volume increase, it was possible to eliminate this phase and obtain an isovolumetric state. The initial and relatively rapid incline of the volume curve during the adrenaline infusion was, however, hardly at all affected by such a procedure. This finding supports the view that the small initial volume increase in all probability reflects an increased blood volume as a consequence of the dilator action of adrenaline. Exactly where within the vascular bed this widening of the capacitance vessels takes place will be discussed below. — Further support of an outward capillary filtration during the adrenaline-induced vasodilatation in the muscles is given by the data in Fig. 20. In *A* and *B* adrenaline and acetylcholine were infused in such amounts as to induce equivalent dilatations of the resistance vessels. Despite the much more pronounced dilator response of the capacitance vessels to acetylcholine, as judged by the initial volume increase of each curve, the slow and continuous second volume increase was, if anything, somewhat smaller during the acetylcholine administration. This would be expected if the slow phase of volume increase really is due to an outward transcapillary filtration, as acetylcholine has such a marked dilator influence also on the capacitance vessels. These vessels are, as has been mentioned, mainly identical with the veins, and as the postcapillary resistance vessels are essentially identical with the small veins, they form an important part also of the capacitance vessels. The more equally a dilator — or constrictor — influence affects both pre- and postcapillary resistances, the less the transcapillary filtration equilibrium will be affected, as long as other factors, like arterial inflow pressure and venous outflow pressure, are kept constant.

In Fig. 20 *C*, where a somewhat bigger dose of adrenaline was given, an

initial *decline* in the volume curve, indicating a constriction of the capacitance vessels, was followed by a slight but continuous *incline*. This second, inclining phase was coincident with the fully developed and steadily maintained dilatation of the resistance vessels. This finding, too, speaks in favour of the above-mentioned interpretation of the changes in volume of the hind parts, as being due to effects on both the capacitance vessels and the capillary filtration exchange. In this very case, the two phenomena affected the volume in *opposite* directions, that is, adrenaline in the used concentration induced a constriction of the capacitance vessels in combination with an outward transcapillary filtration, due to a dilatation of the precapillary resistance vessels.

Admittedly, each of the mentioned analytical steps constitutes only indirect evidence of differential adrenaline effects on the two main consecutive resistance vascular sections within the skeletal muscles. However, as all the findings point to one and the same interpretation, they offer in fact strong support of the view that the second, slow and continuous volume augmentation, recorded during adrenaline infusion at minute concentrations, really is due to an outward filtration of intravascular fluid. Under the prevailing circumstances, this can reasonably be ascribed to an increased capillary hydrostatic pressure, on the basis of a relatively more pronounced dilatation of the precapillary than of the postcapillary resistance vessels.

3. Comments

The present experiments indicate that within the 'physiological' range of sympathetic activity the 'nervous link' is far superior to the 'hormonal' one with regard to inducing constrictor responses. The results are thus in agreement with earlier studies of the sympathetic adrenergic neuro-humoral control of the resistance vessels in different 'parallel-coupled' vascular circuits (Celander 1954). The present study shows that the dominance of the 'nervous link' holds not only for the resistance vessels but also for the 'series-coupled' capacitance vessels; and, in addition, for the sympathetic neuro-hormonal influence on the relation between the pre- and postcapillary resistance to flow. On the other hand, adrenaline, especially in low concentrations, can induce a powerful dilatation of the resistance vessels of the skeletal muscles, a fact well known from many earlier studies (for lit. see for instance Celander 1954, Euler 1956, p. 182). The present analysis of the adrenaline effect on various consecutive vascular sections strongly suggests that its dilator influence is by far most pronounced on the resistance vessels, and here restricted essentially to their precapillary, arterial section. This sugges-

tion is supported firstly by the fact that adrenaline in dilator doses seemed to affect the precapillary resistance section relatively more than the postcapillary one, to judge from the induced *outward* filtration across capillary walls in the skeletal muscles. Secondly, it was also found that when an adrenaline-induced relaxation of the capacitance vessels (mainly the veins) did on the whole occur at all, it was always very slight in comparison with that of the resistance vessels, (mainly the small arterial vessels.) It should be recalled in this connection that the postcapillary resistance vessels—in principle the venules—form a quantitatively important part of the capacitance vessels also, and hence it can be concluded that if *these* resistance vessels really are dilated by adrenaline, this dilatation must be almost insignificant. Quite often a dose of adrenaline that caused a marked blood flow increase induced a *decrease* in the regional blood volume, while, at the same time, there was evidence of a shift in the capillary Starling equilibrium, leading to an outward filtration. Since the term 'capacitance vessels' is a functional one, the arterial side of the vascular bed also contributes to the total 'capacitance' of the vascular bed, though to a minor extent compared with the veins. Undoubtedly, adrenaline dilates the small arterial vessels in the skeletal muscles, and their widening must mean some increase of regional blood volume, other factors being constant. Further, such an arterial vasodilatation must lead to a certain increase of transmural pressure within the subsequent vascular sections, which, in turn, tends to distend the veins passively, causing some increase in their blood content. Such factors may be fully responsible for the small increase in regional blood volume observed during adrenaline infusion at low concentrations. It is therefore likely that the vasodilator action of adrenaline in skeletal muscles is largely confined to the small arterial vessels, while the smooth muscles of the veins, including both the venules — the postcapillary resistance vessels — and the bigger veins, may be throughout *excited* by adrenaline. As a contrast, acetylcholine, known to dilate veins also, caused a considerable increase of regional blood volume, when given in doses that relaxed the resistance vessels to the same extent as did adrenaline. Expressed according to the hypothesis of AHLQUIST (1958) in terms of 'alpha-, beta- and gamma-receptors', the above-mentioned findings should mean that the greater majority of the beta-receptors are located in the smooth muscle cells of the small arterial vessels, while alpha- and gamma-receptors are abundantly present in both the arterial and venous vascular sections.

It might be argued that the smooth muscles of the veins will not be exposed to the same concentration of adrenaline as those of the arterial vessels, since it is known that catechol amines in the lower 'physiological' concentrations

are almost completely eliminated by a single pass through the vascular bed (CELANDER and MELLANDER 1955). However, the smooth muscles of the veins will be reached from the tissue spaces *via* the capillary exchange and, at least the bigger ones *via* their vasa vasorum. Moreover, acetylcholine, known to be eliminated very quickly also (see ROSENBLUETH 1950 p. 88), induced considerable dilatations of the capacitance vessels, including the veins. Noradrenaline induced definite constrictions of the capacitance vessels even when infused in such doses in which adrenaline did not affect the veins. Therefore it seems less likely, although of course not definitely disproved, that the above-mentioned mechanism can explain the finding that veins of a muscle region are not dilated by adrenaline given in minor concentrations.

The fact that direct, graded stimulations of the adrenal medullae caused vascular responses in the hind parts, that generally lay between those obtained when equivalent quantities of noradrenaline or adrenaline alone were infused, calls for some comments. It is known that the adrenal medulla contains both adrenaline and noradrenaline in relationships that vary among the species. In the adult human being adrenaline constitutes up to about 85 to 90 per cent of the total catechol amine content of the adrenal glands (see EULER 1956, p. 118). In the cat, on the other hand, the noradrenaline fraction is often the biggest one. The present results, where all the gland cells were simultaneously activated, are in agreement with this fact, as the vasoconstrictor effects generally prevailed when the glands were excited. However, it appears that the two catechol amines are contained in separate cells, which even seem to have separate innervation (EULER 1956 p. 259). There is evidence that adrenaline cells and noradenaline cells can be more or less selectively activated, depending on the character of the autonomic pattern induced (*e. g.* FOLKOW and EULER 1954, EULER and FOLKOW 1958). Thus, there appear to be circumstances where practically only adrenaline is secreted in the cat also, which justifies the study of the effects of graded infusions of either adrenaline or noradrenaline separately. For such reasons the studied vascular effects of graded stimulations of the adrenal medullary glands and those secondary to infusions of the two catechol amines complement each other, both with regard to the intensity of responses and to their induction of vasoconstriction or vasodilatation.

CHAPTER VI

General comments and conclusions

In earlier studies there are many observations that indicate that not only the arterial side but also the venous side of the systemic circulation is controlled by sympathetic vasoconstrictor fibres and adrenal medullary hormones (for ref. see for instance the reviews by LANDIS and HORTENSTINE 1950, FOLKOW 1955, 1956 a, and FREIS 1960 and the studies by ALEXANDER 1954, 1955, GUYTON et al. 1958, SHADLE, ZUKOF and DIANA 1958). The present study, performed on a skin-muscle region and also on a pure muscle region in the cat, with a technique that afforded possibilities of also examining quantitative aspects of neuro-hormonal vascular control, fully supports this view. The vascular bed was here considered more from a functional than from a morphological point of view, according to the distinction, on a functional basis, of its various 'series-coupled' sections, as was outlined in chapter I. In most previous investigations the interest has been focused on the responses induced *either* in the 'resistance' *or* in the 'capacitance' vessels. By the present approach the differentiated reactions evoked in both the resistance and the capacitance vascular sections were studied *simultaneously*, with possibilities also of quantitative evaluations. Further, the effects on net filtration exchange, secondary to neuro-hormonally induced changes in the ratio of the precapillary to the postcapillary resistances, were also examined.

Most of the experimental findings of this study have already been commented upon in the previous chapters, especially where evaluations of the validity and reliability of the technique and interpretation of the records are concerned. This part of the paper will therefore only present a short survey of the main results, together with some general conclusions and comments.

In chapter II the methods and preparations utilized for measuring the above-mentioned vascular responses have been described in detail. They implied in principle the following: the region studied was in the normal way supplied with blood — oxygenated in the lungs — from the intact heart *via* intact arteries. Thus no artifical pump device was employed, which can markedly affect vascular reactivity (FOLKOW 1952 b). The arterial inflow pressure and venous outflow pressure of the region studied were measured and could be kept constant, and the reactions of the resistance vessels to

vasoconstrictor fibre stimulation and adrenal medullary hormones were determined by way of the induced changes in the rate of venous blood outflow. The responses of the capacitance vessels were deduced from characteristically rapid changes in total volume of the area studied, reflecting the phasic variations of the regional blood content, while intermittent use of an isotope dilution technique gave values for the regional blood volume contained during steady state conditions. Further, owing to certain characteristics of the volume recording, the slower and more continuous fluid shifts across the walls of the capillary exchange vessels, occurring whenever the relation between pre- and postcapillary resistance was changed, could also be followed.

In chapter III, an experimental analysis of the method was undertaken, which elucidated in more detail the potentialities for differentiating quantitatively also, between the various vascular responses to sympathetic discharge. Further the more general question, to what extent the prevailing experimental circumstances may have affected the results, was here discussed.

In chapter IV the sympathetic vasoconstrictor fibre influence was studied, and in chapter V the adrenergic hormonal influence as compared with the direct nervous control, with special regard to the effects induced in the pre- and postcapillary resistance sections and in the capacitance vessels. Electrical stimulation of the sympathetic vasoconstrictor fibres was found to induce prompt constrictions in both the resistance and the capacitance vascular sections, and these fairly rapid responses were begun and fully developed within about the same period of time. Almost the full range of constrictor fibre control of the resistance vessels was covered by discharge rates from 0 up to 8—10 impulses/sec, and definitely maximum effector responses were reached at around 16 impulses/sec. This is in agreement with data presented by FOLKOW (1952 a) and CELANDER (1954). The increases of resistance within the precapillary section were throughout always stronger than those within the postcapillary section, both in absolute and relative terms, leading to a decrease of capillary hydrostatic pressure. With regard to the capacitance vessels, definitely maximum effects were reached at a lower discharge rate than was the case with the resistance vessels, generally already at 8 impulses/sec. Nearly maximal responses were in fact already obtained at stimulation frequencies around 4 impulses/sec, as is the case with the spleen (CELANDER 1954), an organ with a blood depot function like that of the capacitance vessels. The sympathetic adrenergic vasomotor fibre system thus exerts its most differentiated action in the very low frequency range, and this range is definitely most narrow for the capacitance vessels, (see for instance Fig. 8, which summarizes the frequency-response curves for both resistance and capacitance vessels). This means that, in the low frequency

range, even minor changes in sympathetic discharge will markedly affect the blood depot sections of the systemic vascular bed.

The constrictor fibre control of the vascular bed of a skin-muscle region was found to be extensive. It was capable of inducing up to about sevenfold increases in resistance beyond the 'basal tone' level of the resistance vessels, and 'mobilization' of blood up to 30 to 40 per cent of the total blood volume contained at 'basal tone' in the capacitance vessels. The effect on the capacitance vessels seemed to be almost exclusively due to an active contraction of their smooth muscles, and only to a relatively minor extent due to passive-elastic recoil.

From the above-mentioned data concerning the increases of flow resistance and the extent of blood translocation, the induced decrease of internal radius in an 'average' resistance and capacitance vessel could be computed in approximate figures if certain assumptions were made. At the most intense vasoconstrictor fibre activation the luminal reduction of an 'average' resistance vessel was thereby found to amount to roughly 35 per cent, but in an 'average' capacitance vessel only to about 20 per cent. Such a difference seemed to exist at all discharge rates, although it was most pronounced at the highest stimulation frequencies. On closer view this difference does not necessarily mean that the smooth muscles of the resistance vessels (mainly arterial vessels) are more shortened than those of the capacitance vessels (mainly veins), even if this possibility may not be definitely excluded. However, the wall/lumen ratio of the precapillary resistance vessels, being much bigger than that of the veins, implies a pronounced 'potentiating' effect of the wall mass on the luminal decrease induced by a given smooth muscle shortening in the arterial section of the resistance vessels. (For details concerning the implications of differences in vascular wall/lumen ratio see FOLKOW 1956 b, FOLKOW, GRIMBY and THULESIUS 1958). It seems inevitable that such a physical consequence of the known structural differences between arterial and venous vessels must be of considerable importance in this connection. Both the relatively more pronounced luminal reductions of the resistance vessels and the less hyperbolic curve, which characterizes the relation between frequency and their response, can in fact well be explained by their bigger wall/lumen ratio (for further details see chapter IV:1, comments). Further, it may be possible that a plugging by blood cells of a number of the smallest blood vessels can occur during constriction. Such a mechanism may contribute to the increase in regional resistance and hence potentiate the effect on blood flow induced by the smooth muscle contraction *per se* in the resistance vessels.

In comparison with the effects evoked by vasoconstrictor fibre stimula-

tion, the constrictor responses induced by the adrenal medullary hormones were rather weak, being generally only some 20—25 per cent of those caused by the vasoconstrictor fibres (see Fig. 19 and 21). This predominance of the direct nervous link of the sympathetic system has previously been pointed out as regards the control of the resistance vessels (CELANDER 1954), and in this study the same principle was found to apply also to the control of the capacitance vessels. On the other hand, adrenaline, infused in low physiological concentrations, was able to evoke pronounced dilator responses in the resistance vessels, particularly in the pure muscle region, as did the adrenaline component of the catechol amines secreted from the adrenal medullary glands. At the same time, the capacitance vessels were, however, only insignificantly dilated by adrenaline; in most cases adrenaline in fact induced a constriction of these vessels. Acetylcholine had, on the other hand, a most pronounced dilator effect on the capacitance vessels also. It was concluded that the veins of a skeletal muscle region may under normal circumstances only be constricted by adrenaline in all concentrations. Expressed in terms of AHLQUIST's hypothesis (see AHLQUIST 1958), this might be attributed to a very sparse supply of so-called 'beta-receptors' in the smooth muscles of the veins as compared with their supply of 'alpha- and gamma-receptors'. If the adrenaline-induced vasodilatation is essentially indirect, caused by release of lactic acid in the skeletal muscles and a consequent local change in carbon dioxide tension (LUNDHOLM 1958), it can be concluded that this environmental change then has very little effect on the venous section.

The two main variable sections of the resistance vessels seemed to be affected to a different extent when exposed to neuro-hormonal influences. Thus, there was regularly evidence of a relatively more pronounced rise in precapillary than in postcapillary resistance, resulting in a fall of hydrostatic capillary pressure. This conclusion was based on the fact that during a neurohormonal vasoconstriction an absorption of extravascular fluid into the circulatory system regularly occurred, which under the prevailing experimental conditions could reasonably be attributed only to a decrease in mean hydrostatic capillary pressure. The rate of this transcapillary influx became especially marked at the highest stimulation frequencies (6—16 impulses/sec). Also this difference in the extent of luminal narrowing may be ascribed to the previously discussed difference in wall/lumen ratio in the precapillary resistance vessels (small arteries) as compared to the postcapillary ones (small veins). — During adrenaline-induced vasodilatation the precapillary resistance vessels seemed to be relatively more dilated than the postcapillary ones (small veins), then inducing an outward capillary filtration. Besides the influence of differences in wall/lumen ratio, true differences in smooth muscle

reactions may contribute to bring about this phenomenon. As has already been discussed, it seems as if the veins in general are little or not at all dilated by adrenaline. — The results thus make it clear that adrenergic neuro-hormonal factors not only control the haemodynamics of the resistance and the capacitance vessels *per se*, but also that they affect the filtration exchange between the extravascular and intravascular spaces.

With regard to the reactions of the capacitance vessels, it should be noted that these vessels were here throughout studied under circumstances where they were allowed to contract or relax essentially in an isotonic fashion. There can be occasions, however, in the intact organism, *e. g.* in asphyxia, when all the parallel- and series-coupled vascular sections may be activated by a generalized and uniform increase of sympathetic discharge, then leaving little place for true translocations of blood within the circulatory system. Under such circumstances the smooth muscles of the capacitance vessels can be expected to constrict largely isometrically, resulting in an increase of central venous pressure, if the heart does not promptly increase its output, in which case there will be an overall increase of cardiovascular pressure. Further, under certain circumstances, the haemodynamic situation may be such as to allow an intermediate type of the pure isotonic and isometric forms of smooth muscle contraction to appear within the capacitance vessels. It is for such reasons of great importance also to investigate the reactions of the capacitance vessels when they are forced to contract in a relatively pure isometric way, as in the interesting studies of their influence on 'mean circulatory pressure' performed by GUYTON and his group (GUYTON *et al.* 1956, 1958). — On the other hand, in many cardiovascular reaction patterns in the intact organism, as during muscular work, mean central venous pressure varies surprisingly little (HOLMGREN 1956, RUSHMER and SMITH 1959). Such a pattern is evidently so differentiated as to balance the reactions of various parallel- and series-coupled vascular regions, so that vasodilatations in some sections are compensated by constrictions in others, while 'venous return' is enhanced, a situation implying a considerable redistribution of blood. Therefore it seems likely that the reactions of the capacitance vessels — except in the earlier-mentioned situations and, of course, when changes in body position superimpose hydrostatic forces of considerable magnitude —, often do appear as essentially isotonic contractions and relaxations of their smooth muscles, implying definite translocations of blood from capacitance vessels. This view is also in accordance with the findings of RASHKIND *et al.* (1953), ROSE and FREIS (1957) and others, who studied changes in 'venous return' during vasoconstrictor and vasodilator influences. However this may be, the present experiments appear to show that in a skin-muscle region

there is a highly potent adrenergic neuro-hormonal control of the capacitance vessels, the range of which has been quantitatively estimated in terms of amount of blood expelled under circumstances where the smooth muscles contract essentially isotonically. There are good reasons to believe that the frequency-response characteristics estimated here are representative, whether the smooth muscles of the capacitance vessels contract isotonically or isometrically in the intact organism, or in a form between these extremes. The frequency-response curves of, for instance, the nictitating membrane thus show essentially similar characteristics, whether its smooth muscles contract in an isometric or isotonic fashion (see ROSENBLUETH 1950, p. 88).

With regard to the regulation of the circulating blood volume, the vasoconstrictor fibres seem to imply a means of control in three principally different ways: (1) By way of the 'active' constriction of the capacitance vessels, and (2) to a much slighter extent by way of the passive-elastic recoil of these vessels. The latter mechanism is secondary to the regional lowering of the transmural pressure within the capacitance vessels, when the constrictor nerves predominantly affect more proximally situated series-coupled vascular sections. By means of these two mechanisms up to about 35 per cent of the blood volume, contained in the skin-muscle region during 'basal tone' conditions, can be mobilized rapidly. (3) In addition there is a transfer of extravascular fluid into the intravascular compartment, secondary to the lowering of mean capillary pressure along with vasoconstrictor fibre activation. — It is evident that the first-mentioned mechanism is dependent directly on the activation of the smooth muscles of the capacitance vessels, essentially the veins. The two latter mechanisms, on the other hand, are secondary to the dominance of the neuro-hormonal control on the precapillary resistance vessels as compared with the postcapillary ones. Therefore, both the resistance and the capacitance vessels may contribute significantly, but in quite different ways, to the mobilization of fluid for increasing or maintaining the return flow to the heart. Thus cardiovascular nervous control implies not only an influence on the cardiovascular system *per se*, but also — by way of its influence on the ratio of pre- to postcapillary resistance, — a possibility of a central control of capillary fluid filtration exchange by the induced shifts in mean capillary pressure. Other things being equal, uniform increases, or decreases, of vasoconstrictor fibre discharge mean an inward, or outward, transcapillary filtration flow respectively. — It should be recalled in this connection that not only the filtration *pressure* as such can be influenced by the constrictor fibres, but also evidently the size of the capillary *surface* available for this exchange. Earlier studies of oxygen diffusion exchange during sympathetic stimulation are most reasonably inter-

preted as being due to neurogenically induced closures of a fraction of the precapillary sphincters, which thus will decrease the number of capillaries open for flow and hence for normal diffusion (BÜCHERL and SCHWAB 1952). Recent experiments (FOLKOW and MELLANDER 1960) support this view, as it was found that the 'filtration coefficient' appears to decrease markedly on constrictor fibre activation, under circumstances where a constant outward filtration gradient was maintained. The most probable explanation of such a finding is a temporary exclusion of a fraction of the capillaries from the circulation. — Virtually nothing is known of whether normally such vasomotor fibre influences on the transfer of extracellular fluid between the intravascular and extravascular compartments are reflexly controlled *e. g. via* 'volume receptors', situated within the low pressure sections of the vascular system. It is further not known whether differentiated patterns of constrictor fibre discharge in various series-coupled resistance sections of the vascular bed may occur, allowing variations of the ratio between the pre- and postcapillary resistances in both directions, *i. e.* not only so as to increase this ratio, as is the case at a uniform increase of sympathetic constrictor fibre activity. If this were so, it would imply a highly selective constrictor fibre control of capillary fluid filtration exchange. Although such a possibility may not *a priori* appear very likely, it ought to be taken into consideration and the subject may in fact be studied by way of the present technique.

The present finding, that transcapillary 'inward filtration' can become rather marked on constrictor fibre activation, does not at first sight agree with statements that such a type of fluid transfer is relatively insignificant during vasoconstrictions induced by carotid occlusion (GREGERSEN 1940). Howewer, arterial blood pressure is then raised largely in proportion to the raised precapillary resistance, so that capillary pressure should then not be expected to change more significantly. It should further be recalled that in the present experiments the 'extravascular fluid mobilization' was more significant only when the nearly maximal 'physiological' discharge rates were reached. At such high rates practically all the blood volume which can be mobilized from the capacitance vessels has already been translocated. No doubt, the contribution of a more significant 'transfusion' of extravascular fluid would be of great importance for cardiovascular dynamics in situations demanding massive, acute increases of the circulating blood volume. However, this necessitates very intense reflex increases of constrictor fibre activity and such high discharge rates are probably only seen under quite exceptional circumstances. Less intense reflex activation of the vasomotor fibre system, though haemodynamically impressive enough, will hardly be enabled to

induce larger inward fluxes of extravascular fluid within short periods of time, to judge from the estimates of the present study. Further, even at marked increases of sympathetic activity the effect of such a 'transfusion' of extravascular fluid would after all not be too impressive in the *acute* situation, for several reasons. Firstly, as soon as the blood becomes diluted more significantly the process will be self-limiting, by way of the concomitant decrease in colloid osmotic blood pressure. Secondly, the local accumulation of vasodilator 'metabolites' — and the increasing extent of tissue hypoxia along with the reduction of blood flow — will tend to counteract the influence of the constrictor fibres on the vascular smooth muscles, hence again tending to raise mean capillary pressure and open up previously closed capillaries. Thirdly, under such circumstances the capillary wall itself may be damaged by hypoxia, causing some increase of effective pore size so that plasma proteins pass out into the tissue spaces to a greater extent than is normally the case, thus lowering 'net inward filtration pressure'. Fourthly, there is a possibility that postcapillary resistance increases along with the growing tendency towards aggregation of the blood cells at intense reduction of flow, which presumably will increase the regional viscosity of the venous blood and in addition decrease the effective bore of the small veins (cf. GELIN 1956). Other things being equal, such a change in the flow conditions within the postcapillary resistance vessels will tend to raise mean capillary pressure. — Despite all these opposing forces, it seems nevertheless probable that in many circumstances, *e. g.* during extensive blood losses, the neurogenically induced absorption of extravascular fluid might be a highly important factor contributing to the restitution and maintenance of a sufficient 'venous return' in situations of incipient circulatory insufficiency.

The fact that the constriction of the capacitance vessels reaches such relatively intense levels already at quite low rates of sympathetic discharge, as compared with that of the resistance vessels, is of interest also when cardiovascular dynamics are considered more in general. These findings should also be put in relation to the fact that stimulation of the sympathetic fibres of the heart is known to induce by far the most drastic relative increases of heart rate in the lower discharge frequency range (FOLKOW, LÖFVING and MELLANDER 1956). Similarly, the positive inotropic effect on the myocardium seems to be relatively most increased by sympathetic discharge in the low frequency range (SARNOFF 1960). The frequency-response curve concerning the sympathetic effects on the heart is thus placed well to the left of that of the resistance vessels. This differentiated organization of the various cardiovascular neuro-effector units seems well fitted for the purpose of the sympathetic control of the circulation in maintaining an adequate blood flow through-

out the body. Even if an undifferentiated increased discharge takes place within the sympathetic nervous system, as for instance during haemorrhage, the relative extent of the effector responses will vary in accordance with the different slope characteristics of the frequency-response curves of the heart, the capacitance and the resistance vessels. It will have the consequence that the blood reservoirs of the capacitance vessels and also of the spleen are already more or less completely mobilized at slight reflex increases of sympathetic activity, helping to maintain an adequate 'venous return'. Also, quite early in the reflex increase of sympathetic activity both the contraction force of the heart and the heart rate can be expected to be markedly augmented, especially the heart rate perhaps, owing to the concomitant reciprocal decrease of vagal tone. A situation is thus created where a fairly normal cardiac output, and hence blood supply to the tissues, may be maintained, while so far the flow resistance is but little increased. Only when the full mobilization of blood from depot regions and the potentiated heart activity do not suffice to maintain a reasonable cardiovascular equilibrium, and the constrictor fibre discharge therefore is further increased reflexly, can more intense constrictions of the resistance vessels be expected to occur. With this follows a more significant 'mobilization' also of the extravascular fluid, by way of the absorption of extravascular fluid at the capillary level. This more drastic increase of flow resistance will, however, not affect all tissues to the same extent. Since the resistance vessels of, for instance, the brain and the myocardium appear to have only a sparse supply of vasoconstrictor fibres, there will be but little neurogenic influence on the regional resistance of these vascular beds (*e. g.* FOLKOW 1956 a). Consequently, such vitally important tissues may be markedly favoured with regard to blood flow distribution during decreased cardiac output, while the resistance vessels of other parallel-coupled vascular circuits are much more strongly constricted.

So far, no regional differences in sympathetic discharge rate have been implied, but only some functional consequences of the different characteristics of the various cardiovascular neuro-effector units. As already hinted, it might be possible to reveal by means of the present technique, whether in various reflex or centrally induced patterns a differentiation of the discharge rate in the sympathetic fibres of the different vascular sections also takes place, once the quantitative relationships between the responses obtained at known frequencies of fibre discharge are known. For such studies the vasomotor fibre connections between the hind and the main parts of the experimental animal must be left intact, the reflex and centrally induced responses within the various vascular sections quantitatively analysed and then compared with those induced by direct, uniform stimulation of the

constrictor fibres at known rates. The vascular effects of haemorrhage, asphyxia etc. can thus be studied in more detail. Further, studies are in progress, which attempt to reveal whether at least some of the receptors located within the low-pressure sections of the cardiovascular system may more or less selectively control the tone of the capacitance vessels (see FOLKOW *et al.* 1960). Even smaller differences in discharge rate between resistance and capacitance vessels are here of great importance from the haemodynamic point of view. Also, topical stimulations of cortical and hypothalamic sympathetic centres are at present being carried out in order to investigate whether centrally induced vasomotor reactions are to some extent differentiated with regard to the discharge rate in the various series-coupled vascular sections.

Apart from such problems, further aspects of the nervous and humoral control of consecutive sections of the vascular bed can be studied in more detail. Mention may here be made of a few subjects that can be approached by means of the present technique. A study of the neuro-hormonal control of the precapillary 'sphincter vessels', which determine the fraction of capillaries open to flow and hence to normal filtration and diffusion exchange,has already been briefly mentioned (FOLKOW and MELLANDER 1960). — Also the neural influence on the fairly marked distensibility of the capacitance vessels is at present the subject of detailed studies. Under some circumstances, *e. g.* in the erect position, the passive-elastic recoil of these vessels will significantly influence blood distribution and then often in a direction opposite to the reflexly induced vasoconstrictor effects. The interaction between known increases of the venous outflow pressure and the responses of the capacitance vessels to graded stimulations of the constrictor fibres is then analysed. — Further, other recent experiments with this technique indicate that the vasoconstrictor effect of angiotensin is more or less selectively confined to the resistance vessels, presumably to their precapillary section. This substance thus leaves the capacitance vessels relatively unaffected, as compared with *e. g.* noradrenaline (FOLKOW, JOHANSSON and MELLANDER 1960). — Lastly, it seems possible also to analyse in a similar way the vascular reactions involved in reactive hyperaemia (KJELLMER 1960), and those induced by certain vasodilator substances and by the sympathetic vasodilator fibres. — There are thus good reasons to believe that the present technique will permit a number of more detailed analyses of the above-mentioned problems and others related to them, concerning cardiovascular control mechanisms, thereby adding further information not only to knowledge of the organization of the vascular response patterns as such, but also of the functional characteristics of the sympathetic nervous system.

General summary

1. A method is described for investigating in cats the reactions occurring simultaneously in the different 'series-coupled' vascular sections of a skin-muscle region, supplied in the normal way with oxygenated blood from intact lungs, heart and arterial connections. — The arterial inflow pressure and the venous outflow pressure were measured and could be kept constant. Reactions evoked in the 'resistance vessels' were measured quantitatively in terms of changes in the rate of venous blood outflow. The extent of the reactions in the 'capacitance vessels' was deduced from characteristically rapid changes in total volume of the area studied, reflecting the variations in its blood content, while intermittent use of an isotope dilution technique gave values for the blood volume contained when the preparation was in a steady state condition. Characteristically slower changes in the volume of the preparation were found to reflect fluid shifts across the capillary walls, occurring whenever the ratio of pre- to postcapillary resistance was changed.

2. The range of sympathetic adrenergic neuro-hormonal control of the vascular bed was investigated, with special reference to the influence on the pre- and postcapillary resistance vessels and on the capacitance vessels.

3. The frequency-response curve for the capacitance vessels, which was obtained using stimulation strength to ensure excitation of all the vasoconstrictor fibres, was found to be placed to the left of that for the resistance vessels. The maximal response was therefore reached at lower discharge frequencies in the capacitance section than in the resistance section of the vascular bed. This means that at low or moderate discharge rates of the vasoconstrictor fibres the effects were, *in relative terms*, more pronounced in the capacitance than in the resistance vessels.

4. The increase in resistance was always greater in the pre- than in the postcapillary resistance vessels and led to a fall in mean hydrostatic capillary pressure — at maximum discharge rates amounting to some 15 mm Hg — to judge from the influx of extravascular fluid into the circulatory system occurring during vasoconstrictor fibre stimulation.

5. When arterial inflow pressure and venous outflow pressure were kept constant sympathetic vasoconstrictor fibre stimulation at increasing 'physiological' rates induced an 'intravascular fluid mobilization', comprising up to maximally about 35 per cent of the regional blood volume contained at 'basal tone' in the capacitance vessels. This effect, in fact reached already at relatively moderate discharge rates, was mainly due to an active constriction of the capacitance vessels, and passive-elastic recoil of these vessels contributed only a very small part of the effect. The 'extravascular fluid

mobilization', secondary to the relatively stronger increase of precapillary than postcapillary resistance, became considerable only in the higher range of 'physiological' stimulation frequencies, when the 'intravascular fluid mobilization' was already largely completed.

6. The neurogenically induced percentage reduction in the radius of the vascular lumen, calculated in approximate figures, appeared to be considerably more pronounced in the resistance than in the capacitance vessels, especially at higher discharge rates.

7. The characteristic functional differences between the resistance and the capacitance vascular sections mentioned above (3, 4, 5 and 6) may, certainly partly and possibly wholly, be explained by the differences in the wall/lumen ratio between the resistance vessels (mainly thick-walled arterial vessels) and the capacitance vessels (mainly thin-walled veins).

8. Catechol amines in 'physiological' amounts, whether released by graded stimulations of the adrenal medullary nerves or infused into the blood stream, always induced quantitatively much weaker constrictor effects on both the resistance and the capacitance vessels, generally only some 20—25 per cent of those obtained by similarly graded stimulations of the vasoconstrictor fibres. In other respects the hormonal constrictor effects on the resistance and the capacitance vessels showed similar characteristics to those induced by vasoconstrictor fibre stimulation.

9. Adrenaline in small or moderate 'physiological' concentrations, which induced pronounced dilatations of the resistance vessels in the skeletal muscles, only slightly dilated the capacitance vessels or even caused constriction, while dilator drugs like acetylcholine always dilated both these vascular sections to a marked degree. It is therefore questionable whether adrenaline normally has any dilator action on the veins of the skeletal muscles.

10. Some implications of the present findings with regard to circulatory homeostasis are discussed.

Acknowledgements

This investigation was supported by grants from the Faculty of Medicine, University of Göteborg, Sweden and from the European Office, Air Research and Development Command, United States Air Force AF61(052)-286.

AB Hässle, Göteborg, Sweden has generously covered the expenses for the employment of a technician.

This investigation is to a great extent based on the ideas and previous works of Dr B. Folkow, who has been my teacher. I wish to express my sincere gratitude to him for his invaluable help.

References

Ahlquist, R. P., Adrenergic drugs. In Drill, V. A. Pharmacology in Medicine. McGraw-Hill Book Co. Blakiston, 1958. Chapt. 27.

Alexander, R. S., The participation of the venomotor system in pressor reflexes. Circ. Res. 1954. *2*. 405–409.

Alexander, R. S., Venomotor tone in hemorrhage and shock. Circ. Res. 1955. *3*. 181–190.

Bayliss, L. E., Rheology of blood and lymph. In Frey-Wyssling, Deformation and flow in biological systems. North-Holland Publ. Co. Amsterdam. 1952. pp. 552.

Brown, G. L. and J. S. Gillespie, The output of sympathetic transmitter from the spleen of the cat. J. Physiol. (Lond.) 1957. *138*. 81–102.

Burch, G. E. and M. Murtadha, A study of the venomotor tone in a short intact venous segment of the forearm of man. Amer. Heart J. 1956. *51*. 807–828.

Bücherl, E. and M. Schwab, Der Sauerstoffverbrauch des ruhenden Skelettmuskels bei reflektorisch-nervöser Vasokonstriktion. Pflüg. Arch. ges. Physiol. 1952. *254*. 337–343.

Celander, O., The range of control exercised by the 'sympathico-adrenal system'. Acta physiol. scand. 1954. *32*. Suppl. 116. 1–132.

Celander, O. and B. Folkow, A comparison of the sympathetic vasomotor fibre control of the vessels within the skin and the muscles. Acta physiol. scand. 1953. *29*. 241–250.

Celander, O. and S. Mellander, Elimination of adrenaline and noradrenaline from the circulating blood. Nature. 1955. *176*. 973–974.

Davis, D. L. and W. F. Hamilton, Small vessel responses of the dog paw. Amer. J. Physiol. 1959. *196*. 1316–1321.

Donegan, J. F., The physiology of the veins. J. Physiol. (Lond.) 1921. *55*. 226–245.

Duggan, J. J., V. L. Love and R. H. Lyons, A study of reflex venomotor reactions in man. Circulation. 1953. *7*. 869–873.

Euler, U. S. v., Noradrenaline. Charles C. Thomas Publ. Springfield, Ill. 1956. pp. 382.

Euler, U. S. v., and B. Folkow, The effect of stimulation of autonomic areas in the cerebral cortex upon the adrenaline and noradrenaline secretion from the adrenal gland in the cat. Acta physiol. scand. 1958. *42*. 313–320.

Fleisch, A., Venomotorenzentrum und Venenreflexe, Blutdruckszügler und Venenreflexe. Pflüg. Arch. ges. Physiol. 1931. *226*. 393–410.

Folkow, B., Impulse frequency in sympathetic vasomotor fibres correlated to the release and elimination of the transmitter. Acta physiol. scand. 1952 a. *25*. 49–76.

Folkow, B., A critical study of some methods used in investigations on the blood circulation. Acta physiol. scand. 1952 b. *27*. 118–129.

Folkow, B., Nervous control of the blood vessels. Physiol. Rev. 1955. *35*. 629–663.

Folkow, B., The nervous control of the blood vessels. In McDowall, The control of the circulation of the blood. Wm. Dawson and Sons Ltd., London. 1956 a. pp. 257.

FOLKOW, B., Structural, myogenic, humoral and nervous factors controlling peripheral resistance. Hypotensive Drugs. p. 163. A Welcome Foundation Symposium. Pergamon Press, London & New York 1956 b.

FOLKOW, B., The efferent innervation of the cardiovascular system. Verh.dtsch. Ges. Kreislaufforsch. 1959. *25*. 84—96.

FOLKOW, B. and U. S. v. EULER, Selective activation of noradrenaline and adrenaline producing cells in the cat's adrenal gland by hypothalamic stimulation. Circ. Res. 1954. *2*. 191—195.

FOLKOW, B., G. GRIMBY and O. THULESIUS, Adaptive structural changes of the vascular walls in hypertension and their relation to the control of the peripheral resistance. Acta physiol. scand. 1958. *44*. 255—272.

FOLKOW, B., B. JOHANSSON and S. MELLANDER, A comparison of the effects of noradrenaline and angiotensin on the resistance and the capacitance vessels in cats. Acta physiol. scand. 1960. *50*. Suppl. 175. 50—51.

FOLKOW, B., B. JOHANSSON, S. MELLANDER and B. ÖBERG, Aspects of the reflexogenic control of the capacitance vessels. Acta physiol. scand. 1960. *50*. Suppl. 175. 51—52.

FOLKOW, B. and B. LÖFVING, The distensibility of the systemic resistance blood vessels. Acta physiol. scand. 1956. *38*. 37—52.

FOLKOW, B., B. LÖFVING and S. MELLANDER, Quantitative aspects of the sympathetic neuro-hormonal control of the heart rate. Acta physiol. scand. 1956. *37*. 363—369.

FOLKOW, B. and S. MELLANDER, Aspects of the nervous control of the precapillary sphincters with regard to the capillary exchange. Acta physiol. scand. 1960. *50*. Suppl. 175. 52—54.

FREIS, E. D., Hemodynamics of hypertension. Physiol. Rev. 1960. *40*. 27—54.

GAUER, O. H., Die Wechselbeziehungen zwischen Herz- und Venensystem. Verh. dtsch. Ges. Kreislaufforsch. 1956. *22*. 61—78.

GAUER, O. H. and J. P. HENRY, Beitrag zur Homöostase des extraarteriellen Kreislaufs. Klin. Wschr. 1956. *34*. 356—366.

GELIN, L.-E., Studies in anemia of injury. Acta chir. scand. 1956. Suppl. 210. 5—130.

GLOVER, W. E., A. D. M. GREENFIELD, B. S. L. KIDD and R. F. WHELAN, The reactions of the capacity blood vessels of the human hand and forearm to vaso-active substances infused intra-arterially. J. Physiol. (Lond.) 1958. *140*. 113—121.

GRAY, S. J. and K. STERLING, Determination of circulating red cell volume by radioactive chromium. Science. 1950. *112*. 179—180.

GREEN, H. D., Circulatory system: Physicals principles. In GLASSER, O., Medical Physics. Chicago, Year Book Publ. 1950. *2*. pp. 1227.

GREGERSEN, M. I., Some effects of reflex changes in blood pressure on plasma volume. Amer. J. Physiol. 1940. *129*. P 369—P 370.

GUYTON, A. C., A. W. LINDSEY, B. ABERNATHY and J. B. LANGSTON, Mechanism of the increased venous return and cardiac output caused by epinephrine. Amer. J. Physiol. 1958. *192*. 126—130.

GUYTON, A. C., A. W. LINDSEY and G. G. ARMSTRONG, Relationship of total peripheral resistance to the pressure gradient from the arteries to the veins. Amer. J. Physiol. 1956. *186*. 294—298.

HAYNES, R. H., The rheology of human blood in glass capillaries. Rev. canad. Biol. 1956. *15*. 255—256.

HOLMGREN, A., Circulatory changes during muscular work in man with special reference to arterial and central venous pressures in the systemic circulation. Scand. J. Clin. and Lab. Invest. 1956. *8.* Suppl. 24.1—97.

KELLY, W. D. and M. B. VISSCHER, Effect of sympathetic nerve stimulation on cutaneous small vein and small artery pressures, blood flow and hindpaw volume in the dog. Amer. J. Physiol. 1956. *185.* 453—464.

KJELLMER, I., Some aspects of work hyperemia in skeletal muscles. Acta physiol. scand. 1960. *50.* Suppl. 175. 85—86.

KNISLEY, W. H., M. S. MAHALEY, Jr. and H. H. JETT, Approximation of 'total vascular space' and its distribution in three sizes of blood vessels in rats by plastic casts. Circ. Res. 1958. *6.* 20—25.

LANDIS, E. M. and J. C. HORTENSTINE, Functional significance of venous blood pressure. Physiol. Rev. 1950. *30.* 1—32.

LEE, J. S. and M. B. VISSCHER, Microscopic studies of skin blood vessels in relation to sympathetic nerve stimulation. Amer. J. Physiol. 1957. *190.* 37—40.

LEVY, M. N., Influence of anomalous blood viscosity on resistance to flow in the dog's hind limb. Circ. Res. 1956. *4.* 533—539.

LUNDHOLM, L., The mechanism of the vasodilator effect of adrenaline. II. Influence of anesthetics on the depressor, pressor and lactic acid stimulating effects of adrenaline. Acta physiol. scand. 1957. *40.* 344—366.

LUNDHOLM, L., The mechanism of the vasodilator effect of adrenaline. III. Influence of adrenaline, noradrenaline, lactic acid and sodium lactate on the blood pressure and cardiac output in unanesthetized rabbits. Acta physiol. scand. 1958. *43.* 27—50.

LÖFVING, B. and S. MELLANDER, Some aspects of the basal tone of the blood vessels. Acta physiol. scand. 1956. *37.* 134—141.

MELLANDER, S., Neuro-hormonal control of consecutive vascular sections. Acta physiol. scand. 1960. *50.* Suppl. 175. 104—105.

MILNOR, W. R. and C. A. BERTRAND, Estimation of venous blood volume in the dog by the indicator-dilution method. Circ. Res. 1958. *6.* 55—59.

PAGE, E. B., J. B. HICKAM, H. O. SIEKER, H. D. MCINTOSH and W. W. PRYOR, Reflex venomotor activity in normal persons and in patients with postural hypotension. Circulation. 1955. *11.* 262—270.

PAPPENHEIMER, J. R., Passage of molecules through capillary walls. Physiol. Rev. 1953. *33.* 387—423.

PAPPENHEIMER, J. R. and A. SOTO-RIVERA, Effective osmotic pressure of the plasma proteins and other quantities associated with the capillary circulation in the hindlimbs of cats and dogs. Amer. J. Physiol. 1948. *152.* 471—491.

RASHKIND, W. J., D. H. LEWIS, J. B. HENDERSON, D. F. HEIMAN and R. B. DIETRICK, Venous return as affected by cardiac output and total peripheral resistance. Amer. J. Physiol. 1953. *175.* 415—423.

REIGHARD, J., H. S. JENNINGS and R. ELLIOTT, Anatomy of the cat. Henry Holt Co. New York. 1949. pp. 486.

ROSE, J. C. and E. D. FREIS, Alterations in systemic vascular volume of the dog in response to hexamethonium and norepinephrine. Amer. J. Physiol. 1957. *191.* 283—286.

ROSENBLUETH, A., The transmission of nerve impulses at neuroeffector junctions and peripheral synapses. Technology Press and Wiley, New York. 1950, pp. 325.

Rushmer, R. F. and O. A. Smith Jr., Cardiac control. Physiol. Rev. 1959. *39*. 41–68.

Salzman, E. W., Reflex peripheral venoconstriction induced by carotid occlusion. Circ. Res. 1957. *5*. 149–152.

Sarnoff, S. J., In H. Schaefer. Central control of cardiac function, Discussion. Physiol. Rev. 1960. *40*. Suppl. 4.232–245.

Shadle, O. W., M. Zukof and J. Diana, Translocation of blood from the isolated dog's hindlimb during levarterenol infusion and sciatic nerve stimulation. Circ. Res. 1958. *6*. 326–333.

Wallace, J. M. and E. A. Stead Jr., Spontaneous pressure elevations in small veins and effects of norepinephrine and cold. Circ. Res. 1957. *5*. 650–656.

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p. 60. Fig. 19, except for legend, is to be exchanged for Fig. 21.

p. 63. Fig. 21, except for legend, is to be exchanged for Fig. 19.

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